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(21) International Application Number: PCT/US93/04807 (22) International Filing Date: 20 May 1993 (20.05.93) (30) Priority data: 887,725 21 May 1992 (21.05.92) US (71) Applicant: RESEARCH CORPORATION TECHNOLOGIES, INC. [US/US]; 101 N. Wilmot Road, Suite 600, Tucson, AZ 85711-3335 (US). (72) Inventors: CUSHMAN, Mark, S. ; 1715 Maywood Drive, West Lafayette, IN 47906 (US). HAMEL, Ernest ; 5200 Benton Avenue, Bethesda, MD 20892 (US). (74) Agent: SCOTT, Anthony, C.; Scully, Scott, Murphy & Presser, 400 Garden City Plaza, Garden City, NY 11530 (US).		(81) Designated States: AU, CA, JP, KR, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: STILBENE DERIVATIVES AS ANTICANCER AGENTS (57) Abstract The present invention relates to stilbene derivatives which possess utility as anti-cancer agents. The compounds can be used to treat cancers which are susceptible to treatment therewith, and can be utilized in a method of treating such cancers. Pharmaceutical compositions containing the compounds are disclosed. Three preferred compounds among those disclosed are (Z)-1-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene, (Z)-1-(4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene, and 4-methyl-3',4',5'-trimethoxybenzylaniline hydrochloride.		

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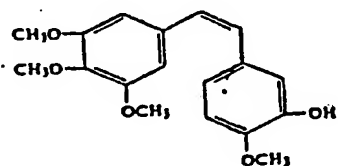
STILBENE DERIVATIVES AS ANTICANCER AGENTS

1 The present invention relates to the use of
stilbene derivatives and stilbene-like derivatives as
anti-cancer agents, pharmaceutical compositions of these
compounds and to novel compounds thereof.

5 Tropical and subtropical shrubs and trees of
the Combretaceae family represent a potentially
unexplored source of new compounds which have useful
biological properties. For example, the genus
Combretum is known in the medical practices of Africa
10 and India for treating various illness such as leprosy
and cancer. However, only a few species like Combretum
micranthum and Combretum zeyheri have received any
substantial scientific work.

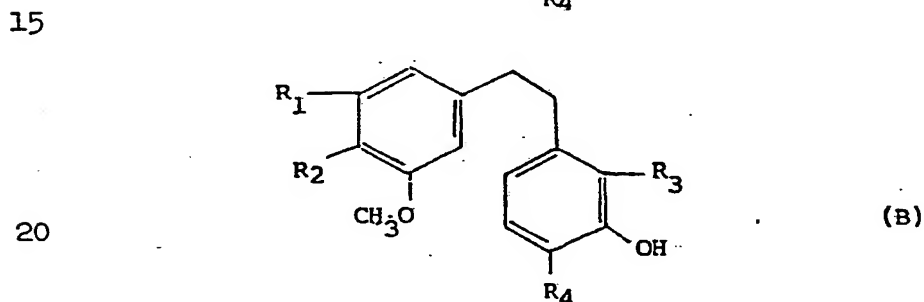
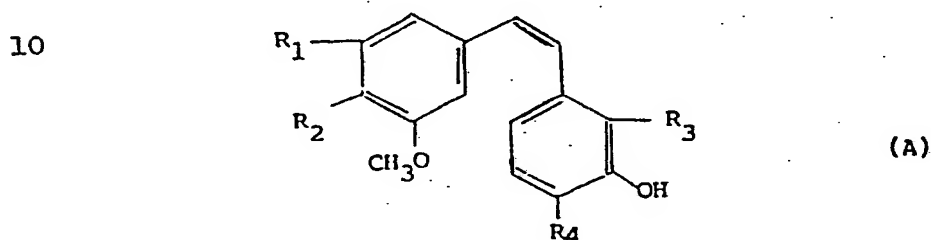
15 In recent years through the work of the U.S.
National Cancer Institute, the African tree Combretum
caffrum has been found to contain certain agents which
were determined to be highly cytotoxic. These agents
isolated from the African tree Combretum caffrum are
referred to as combretasatins.

20 U.S. Patent No. 4,996,237 to Pettit et al.
relates to the isolation and syntheses of a neoplastic
substance having the structural formula:



1 The natural product having such a formula has
been referred to as "Combretasatin A-4". It has been
observed that this cis-stilbene exhibits strong
cytotoxic activity by inhibiting tubulin polymerization.

5 European Patent Application No. 276,051 to
Pettit et al. relates to the isolation, structural
elucidation and synthesis of new antineoplastic
compounds having the structural formulas:

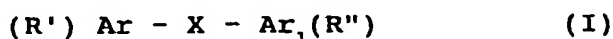


25 wherein R_1 is OH or OCH_3 ; R_2 is H or OCH_3 ; or R_1 and R_2
taken together is $-OCH_2O-$; R_3 is H or OH; and R_4 is OH or
 OCH_3 and wherein the configuration of the double bond in
formula (A) is cis. These compounds were tested to
determine their murine 388 lymphocytic leukemia
30 inhibition.

1 Despite their potential use as anti-cancer
agents, these combretasatin derivatives are limited by
their relatively low solubility in water and saline.
This has led to an increased interest in the syntheses
and evaluation of polymethoxylated stilbenes and
5 dihydrostilbenes as potential anti-cancer agents.

Thus, the present invention is directed to the
development of new anti-cancer agents based on these
natural products as structural leads. More
specifically, the present invention is directed to
10 compounds having two aryl or heteroaryl groups or
combinations thereof separated by a bridging unit of at
least 1 or 2 atoms, such as C=O, alkylene,
alkyleneamino, carboxamido (or derivatives thereof), or
alkene (e.g., ethenes), in which the aryl or heteroaryl
15 groups are substituted by at least two alkoxy groups.
The present invention is also directed to pharmaceutical
compositions thereof and their use as anti-cancer
agents. In an embodiment, the present invention relates
to a series of cis-, trans- and dihydro- stilbenes and
20 N-arylbenzylamines, and aryl benzoamides and the
compounds thereof as anti-cancer agents to be
administered to animals.

The present invention is directed to the use
of compounds having the structural formula (I):
25



and pharmaceutically acceptable salts thereof
wherein Ar and Ar₁ are independently aryl or heteroaryl;
30 and Ar may be mono, di, tri, or tetrasubstituted with R'

1 and Ar₁ may be mono, di, tri, or tetrasubstituted with R";

5 X is $\text{-}\overset{\text{O}}{\parallel}\text{C-}$, $\text{-NH-CH}_2\text{-}$, $\text{-CH}_2\text{NH-}$, $\text{-NH-}\overset{\text{O}}{\parallel}\text{C-}$, $\text{-C-}\overset{\text{O}}{\parallel}\text{NH-}$, $\text{-(Y}_2\text{)(Y}_3\text{)C-C(Z}_2\text{)(Z}_3\text{)-}$ or cis or trans ethylene radical of the formula $\text{-(Y}_1\text{)C=C(Z}_1\text{)}$, CH₂ or CHOH;

Y₁, Y₂, Y₃, Z₁, Z₂ and Z₃ are independently hydrogen, lower alkyl, lower alkoxy, carboxy, lower carbalkoxy, COONR₁₃R₁₄, cyano, or COOQNR₁₅R₁₆;

10 R₁₃, R₁₄, R₁₅ and R₁₆ are independently hydrogen or lower alkyl;

Q is lower alkylene;

each R' may be the same or different and consists of R₁, R₂, R₃ and R₄, and each R" may be the same or different and consists of R₅, R₆, R₇ and R₈;
 15 wherein each R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ are independently hydrogen, lower alkyl, aryl, halo, amino, lower alkylamino, diloweralkylamino, lower alkoxy, lower aralkyl, arylkoxy, lower aralkoxy, cyano, aryloxy, mercapto, lower alkylthio, amino lower alkyl, carboxy,
 20 carbolower alkoxy, CONHR₉, NHCO(R₉), lower alkanoyl, nitro, CF₃, lower alkyl carbonyloxy, amino lower alkoxy, lower alkyl amino lower alkoxy, dilower alkylamino lower alkoxy amino lower alkylene oxycarbonyl, lower alkylamino loweralkyleneoxycarbonyl, dilower alkylamino
 25 lower alkenene oxy carbonyl, OSi(R₁₀R₁₁R₁₂) or Si(R₁₇)(R₁₈)(R₁₉) and at least two of R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ is loweralkoxy;

R₉ is hydrogen or lower alkyl;

30 R₁₀, R₁₁, R₁₇, R₁₈ and R₁₉ are independently lower alkyl; and

1 R_{12} is lower alkyl or lower alkoxy;
and the pharmaceutical composition containing these
compounds as the active ingredients thereof. Also, the
invention relates to novel compounds encompassed by
Formula I.

5 As described hereinabove, the present
invention encompasses compounds of the formula



10 and pharmaceutically acceptable salts thereof wherein
 R' , R'' , Ar , Ar_1 and X are as defined hereinabove. As
defined herein, the Ar group is substituted by R_1 , R_2 , R_3
and R_4 while Ar_1 is substituted by R_5 , R_6 , R_7 and R_8 . In
15 other words, Ar and Ar_1 can independently be
unsubstituted, monosubstituted, disubstituted,
trisubstituted or tetrasubstituted; however the compound
of Formula I must contain at least two alkoxy groups and
preferably at least three alkoxy groups. The alkoxy
groups may be substituted as only Ar or Ar_1 or may be
20 substituted as both Ar and Ar_1 . In an especially
preferred embodiment, at least two of the alkoxy groups
are substituted on Ar ; and in a most preferred
embodiment, at least three of the alkoxy groups are
substituted on Ar_1 .

25 As defined herein, the present invention
contemplates employing the compounds in Formula I in
compositions to be administered in an effective dosage
amount to animals as potential new anti-cancer agents.

30 The term "aryl", when used alone or in
combination, refers to an aromatic group which contains
from 6 up to 18 ring carbon atoms and up to a total of

25 carbon atoms and includes the polynuclear aromatics.
1 These aryl groups may be monocyclic, bicyclic, tricyclic
or polycyclic and are fused rings. Polynuclear aromatic
compound is meant to encompass bicyclic, tricyclic fused
aromatic ring systems containing from 10-18 ring carbon
5 atoms and up to a total of 25 carbon atoms. The aryl
group includes phenyl, and the polynuclear aromatics
e.g., naphthyl, anthracenyl, phenanthrenyl, azulenyl and
the like. The preferred aryl group is naphthyl and
especially phenyl.

10 The term "heteroaryl", when used alone or in
combination, is a nitrogen, sulfur or oxygen containing
heteroaromatic group. The ring heteroatoms are either
nitrogen, sulfur or oxygen. The heteroaryl groups may
be monocyclic, bicyclic, or polycyclic; but if it
15 contains more than 1 ring, the rings are fused.
Furthermore, the heteroaryl groups are planar. The
heteroaryl groups contain 1-4 ring heteroatoms and from
5-14 ring atoms. The heteroaryl group contains from 1-
13 and preferably 3-13 ring carbon atoms and up to a
20 total of 18 carbon atoms. The heteroaryl includes such
groups as thienyl, benzothienyl, naphthathienyl,
thianthrenyl, furyl, benzofuryl, pyrrolyl, imidazolyl,
pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl,
indolyl, indazolyl, purinyl, quinolyl, isoquinolyl,
25 thiazolyl, isothiazolyl, oxazolyl, isooxazolyl,
benzoxazolyl; benzoxathiazolyl, benzothiazolyl and
benzoisothiazolyl, and the like, and the N-oxides of the
nitrogen containing heteroaryl, such as the N-oxides of
pyridyl, pyrazinyl, pyrimidinyl and the like. The
30 preferred heteroaryl groups contain up to 10 ring atoms

1 and 1 or 2 ring heteroatoms and up to a total of 15
carbon atoms. Preferably, the heterocyclic
group contains at least 1 ring nitrogen atom. Preferred
heteroaryl groups include pyridyl, pyrimidinyl,
5 pyrazinyl, pyridazinyl, thienyl, furyl, oxazolyl,
thiazolyl, benzooxazolyl, imidazolyl, indolyl, quinolyl,
isoquinolyl, thiazolyl, benzothiazolyl, benzoxazolyl and
pyrrolyl. The especially preferred heteroaryl groups
include thienyl, pyrazinyl, pyrimidinyl, pyridyl,
10 thiazolyl, and the N-oxide of pyridyl. The most
preferred heteroaryl group is pyridyl.

The alkyl groups when used alone or in
combination with other groups, are lower alkyl contain
from 1 to 6 carbon atoms and may be straight chained or
15 branched. These groups include methyl, ethyl, propyl,
isopropyl, butyl, isobutyl, tertiary butyl, pentyl,
hexyl, and the like.

The preferred alkyl groups contain 1-4 carbon
atoms; more preferred alkyl groups contain 1-3 carbon
atoms. The most preferred alkyl group is methyl.
20 Alkylene as used herein refers to a bridging alkyl group
of the formula C_nH_{2n} . Examples include CH_2 , $-CH_2CH_2-$,
 $-CH_2CH_2CH_2-$ and the like.

As used herein, the term "lower alkoxy" refers
to -O- alkyl groups, wherein alkyl is as defined
25 hereinabove. The alkoxy group is bonded to the main
chain, aryl or heteroaryl group through the oxygen
bridge. The alkoxy group may be straight chained or
branched; although the straight-chain is preferred.
Examples include methoxy, ethyloxy, propoxy, butyloxy,
30 t-butyloxy, i-propoxy, and the like. Preferred alkoxy
groups contain 1-4 carbon atoms, especially preferred

1 alkoxy groups contain 1-3 carbon atoms. The most preferred alkoxy group is methoxy.

"Lower carbalkoxy" is a group of the formula

5 $\begin{array}{c} \text{O} \\ \parallel \\ \text{C-O-Alkyl} \end{array}$, wherein the acyl group is bonded to the main chain and alkyl is as defined hereinabove. Examples include COOMe, COOEt, COOPr, and the like. The preferred group is COOMe.

"Halo" includes fluoro, bromo, chloro or iodo.

10 "Lower Alkylamino" refers to a group wherein one alkyl group is bonded to an amino nitrogen, i.e., NH(alkyl). The NH is the bridge connecting the alkyl group to the aryl or heteroaryl. Examples include NHMe, NHET, NHPr, and the like.

15 Similarly, "lower diloweralkylamino" refers to a group wherein two alkyl groups, which may be the same or different are bonded to an amino nitrogen and the dialkylamino group is bonded to the aryl or heteroaryl through an NH bridge. It is preferred that both alkyl groups are the same. Examples include NMe₂, N(Me)(Et),
20 NEt₂, and the like, the most preferred is NMe₂.

As used herein, "lower arylalkyl", when used alone or in combination, refers to an aryl-alkylene bond, i.e., the aryl alkyl group is bonded as a
25 substituent through the alkylene moiety. Examples include benzyl, phenethyl, phenpropyl, phenisopropyl, phenbutyl, and the like, diphenyl methyl, 1,2-diphenyl methyl, and the like.

The arylalkoxy refers to an O-aryl group wherein the arylalkoxy group is attached as a
30 substituent through an oxygen bridge. Similarly, aralkoxy refers to an O-arylalkyl group wherein the

1 aralkoxy is attached as a substituent through the oxygen atom.

"Alkylthio" refers to an S-alkyl group, wherein the alkylthio is attached as a substituent through the S atom.

5 The term amino lower alkyl refers to a group of the formula alkylene-NH₂, wherein this group is attached as a substituent through the alkylene moiety. Examples include -CH₂NH₂, CH₂CH₂NH₂ and the like.

10 As used herein, lower alkenoyl refers to a lower alkyl group, as defined, wherein one of the carbon atoms is replaced by a carbonyl group. It also includes formyl. Examples include acetyl, propanoyl, butanoyl, and the like.

15 The term "lower alkyl carbonyloxy" refers to a group of the formula O-C-Alkyl, wherein the alkyl is defined herein. In other words, the lower alkyloxy-carbonyl is bonded as a substituent through the oxygen atom. Examples include OC-CH₃, O-C-CH₂CH₃,

20
$$\begin{array}{c} \text{O} \\ \parallel \\ \text{O}-\text{C}-(\text{CH}_2)_2\text{CH}_3 \end{array}$$
 and the like, with the preferred group being OAc.

25 As used herein the term "amino lower alkoxy" refers to the group -O-Alkylene-NH₂-, wherein alkylene is defined hereinabove. This group is attached as a substituent through its oxygen atom. Similarly, the term lower alkylamino loweralkoxy refers to an amino lower alkoxy group, wherein one of the amino hydrogens
30 is replaced by a lower alkyl group. Furthermore, a diloweralkyl amino lower alkoxy refers to an amino lower

1 alkoxy group wherein both amino hydrogens are replaced
 by an alkyl group. The alkyl groups in the latter term
 may be the same or different but it is preferred that
 the alkyl groups are the same. Examples of the first
 term include $O-(CH_2)_2NH_2$, OCH_2NH_2 , and the like; examples
 5 of the second term include OCH_2CH_2NHMe , OCH_2CH_2NHet ,
 OCH_2NHMe , OCH_2NHet , and the like, finally, examples of
 the latter term include $OCH_2CH_2NMe_2$, $OCH_2CH_2NEt_2$, and the
 like.

10 The term "amino lower alkylene oxy carbonyl"
 as used herein, refers to the group $C-O-alkylene-NH_2$

$$\begin{array}{c} || \\ O \end{array}$$

wherein alkylene is as defined herein. Similarly,
 "lower alkyl amino lower alkylene carbonyl" refers to an
 15 amino lower alkylene oxycarbonyl wherein one of the
 amino hydrogens is replaced by an alkyl group as defined
 herein. Furthermore, diloweralkyl amino lower alkylene
 oxycarbonyl refers to an amino loweralkylene oxycarbonyl
 wherein both amino hydrogens are replaced by a lower
 20 alkyl, and the lower alkyls may be the same or
 different. Examples of the first group include
 $-COO-(CH_2)_2NH_2$, $-COOCH_2NH_2$ and the like; examples of the
 second group include $COOCH_2NHMe$, $COOCH_2NHet$,
 $COO(CH_2)_2NHMe$, $COO(CH_2)_2NHet$ and the like, while examples
 25 of the latter group include $COOCH_2NMe_2$, $COOCH_2NEt_2$,
 $COO(CH_2)_2NEt_2$, $COO(CH_2)_2NMe_2$ and the like.

The preferred value of X as used herein is

$$\begin{array}{c} C-NH, \quad NHC, \quad CH_2NH_2, \quad NH_2CH, \quad \text{cis or trans} - (Y_1)C=C(Z_1) \\ || \quad \quad \quad || \\ O \quad \quad \quad O \end{array}$$

 30 and $(Y_2)(Y_3)C-C-(Z_2)(Z_3)$, wherein Y_1, Y_2, Y_3, Z_1, Z_2 and Z_3
 are defined hereinabove. A more preferred value of X is

1 $(Y_1)C=C(Z_1)$, $\begin{array}{c} \text{C-NH} \\ \parallel \\ \text{O} \end{array}$, $\begin{array}{c} \text{NHC} \\ \parallel \\ \text{O} \end{array}$, CH_2NH or CH_2NH . Especially

preferred X is $\begin{array}{c} \text{C-NH} \\ \parallel \\ \text{O} \end{array}$, $\begin{array}{c} \text{NHC} \\ \parallel \\ \text{O} \end{array}$, CH_2NH , NHCH_2 and cis

5 $(Y_1)C=C(Z_1)$. A more especially preferred value of X is

$\begin{array}{c} \text{O} \\ \parallel \\ \text{CNH} \end{array}$, CH_2NH and cis $(Y_1)C=C(Z_1)$, and the most preferred value of X is cis $(Y_1)C=C(Z_1)$ and CH_2NH .

The preferred values of Y_1 and Z_1 in
10 $(Y_1)C=C(Z_1)$ in either the trans or cis forms are independently hydrogen, carboxy, carboloweralkoxy, COONHR_{13} , cyano or $\text{COOQNR}_{15}\text{R}_{16}$. It is preferred that Y_1 is hydrogen, carboxy, carboloweralkoxy, COONHR_{13} , or
15 $\text{COOQNR}_{15}\text{R}_{16}$, and that Z_1 is hydrogen or COOH . More especially, it is preferred that Y is COOH , COOMe , COONHMe , COONHEt , $\text{COO}(\text{CH}_2)_2\text{NEt}_2$, $\text{COOCH}_2\text{NMe}_2$ or H. The most preferred value of Y_1 and Z_1 is hydrogen.

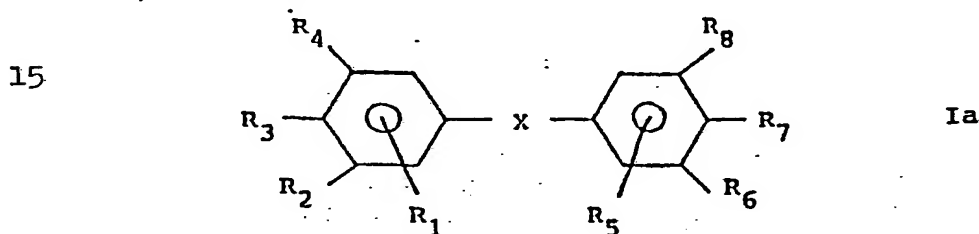
The most preferred values of Z_2 , Z_3 , Y_2 and Y_3 are independently hydrogen, cyano or carboloweralkoxy
20 (e.g. COOMe). It is most preferred that one of Y_2 , Z_2 , Y_3 or Z_3 is hydrogen and the other is hydrogen, cyano or carboloweralkoxy. It is most preferred that Y_2 and Z_2 are hydrogen, Y_3 is cyano or hydrogen and Z_3 is hydrogen, cyano or lower carbalkoxy (e.g., COOMe). It is most
25 especially preferred that Z_2 , Z_3 , Y_2 and Y_3 are all hydrogen.

A preferred value of R_{13} is hydrogen; the preferred values of R_{14} , R_{15} and R_{16} are methyl or ethyl.
30 It is preferred that R_{15} and R_{16} are the same and that both are methyl and ethyl.

The preferred value of Q is ethylene.

The preferred values of $R_1, R_2, R_3, R_4, R_5, R_6, R_7$ and R_8 are independently hydrogen, C_1-C_4 lower alkoxy, benzyloxy, acetyloxy, t-butyl dimethoxy siloxy, halogen, C_{1-4} lower alkyl, t-butyl dimethyl silyloxy, trimethyl silyl, amino, 3-6 dimethylamino lower alkoxy halo (e.g., chloro, bromo), nitro, NMe_2 , C_{1-4} alkylthio, C_{1-4} lower alkyl, $O(CH_2)_2NMe_2$, $O(CH_2)_2NEt_2$. It is more preferred that $R_1, R_2, R_3, R_4, R_5, R_6, R_7$ and R_8 are independently hydrogen, methoxy, chloro, bromo, nitro, $OSi(t-Bu)(CH_3)_2$, NMe_2 , OAc , OEt , OPr , SMe , Me , Et , iPr , $t-Bu$, NH_2 , $NHCOCH_3$, $O(CH_2)_2NMe_2$, and $O(CH_2)_2NEt_2$.

In the most preferred embodiment, the compounds of Formula I have the formula

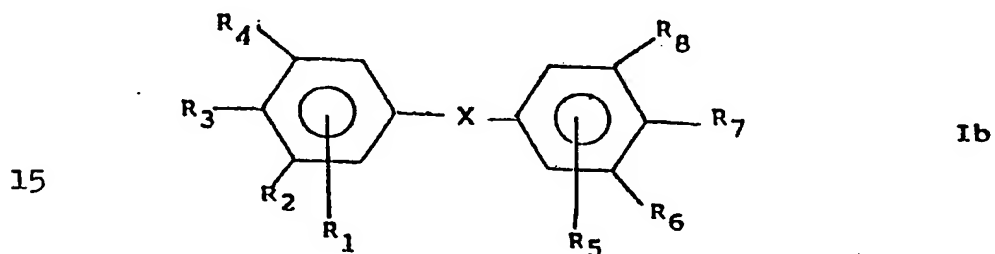


20 In Formula Ia, it is preferred that at least one of R_2, R_3 and R_4 is lower alkoxy, especially methoxy, it is more preferred that at least two of R_2, R_3 and R_4 is lower alkoxy; especially methoxy and it is most especially preferred that R_2, R_3 and R_4 are lower alkoxy (e.g. methoxy). Further, it is preferred that R_1 is hydrogen.

25 Further, it is preferred that at least one of R_6, R_7 and R_8 is other than hydrogen, and most preferably it is preferred that R_6 and R_8 are hydrogen. The most preferred values of R_7 is hydrogen, halo (e.g., chloro, bromo or iodo), lower alkoxy (e.g., OMe , OEt , OPr),

1 diloweralkylamino (e.g., NMe_2), loweralkylthio (e.g.,
SMe), lower alkyl, or CF_3 . In addition, it is preferred
that R_5 is hydrogen; however, if it substituted, it is
preferred that R_5 may be the 2-substituent, and the
5 preferred R_5 value at the 2-position is hydrogen or halo
(e.g., Cl). It is most preferred that R_7 has the
preferred embodiment described herein that R_6 and R_8 are
H and that R_5 is hydrogen or 2-halo (e.g., Cl).

10 An even more preferred embodiment of the
present invention has the formula:



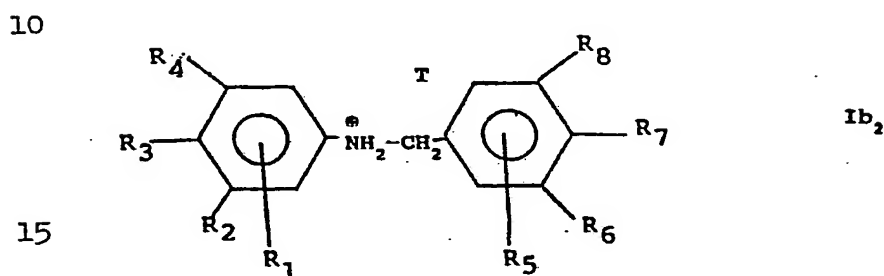
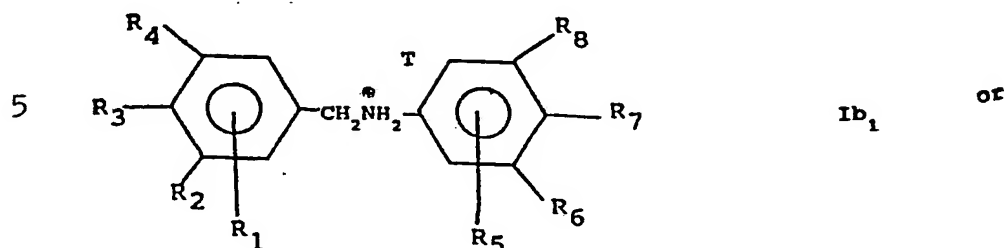
20 or pharmaceutically acceptable salts thereof wherein R_1 ,
 R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , or R_8 are as defined hereinabove and
X is defined as NHCH_2 and more preferably CH_2NH . In this
embodiment, the pharmaceutically acceptable salts are

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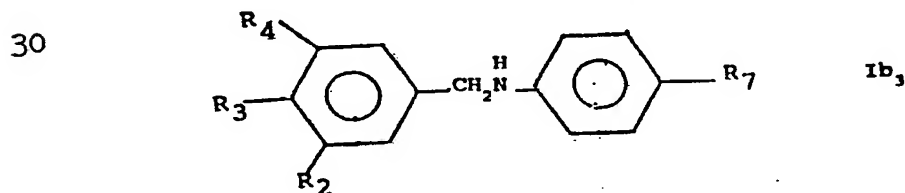
1 also preferred, i.e, wherein the nitrogen in the
 1 bridging group forms a quaternary ammonium ion:



wherein T is the counterion. The counterions include
 such groups as the halides (I, Cl, Br or F), sulfates,
 nitrates, benzenesulfonates, toluene sulfonates,
 20 acetates, propionates, formates, malates, tartrates, and
 the like. The most preferred counterions are the
 halides, especially bromides and more especially
 chlorides.

25 In the compounds of the above formulae, it is
 preferred that R₅, R₆ and R₈ are hydrogen and that R₇ is
 other than hydrogen.

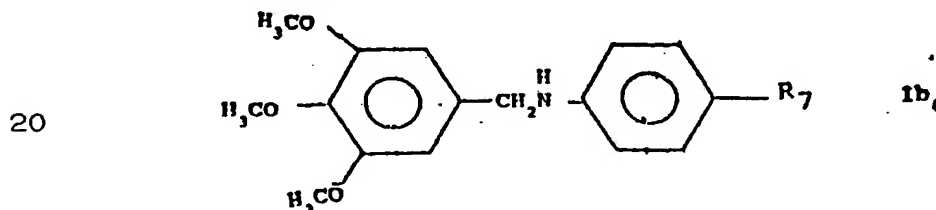
An even more preferred embodiment of the
 compounds of Formulae Ib, Ib₁, and Ib₂ is



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1 or pharmaceutically acceptable salts thereof wherein R_2 ,
 R_3 , R_4 and R_7 are as defined herein. It is preferred
 that R_2 , R_3 and R_4 are lower alkoxy and R_7 is lower
 alkoxy, lower alkyl, halo, thiolower alkyl,
 5 trifluoromethyl, lower carbalkoxy, carboxy, cyano, lower
 alkanoyl, formyl, nitro or sulfonic acid (SO_3H). It is
 most preferred that R_2 , R_3 and R_4 are lower alkoxy, and
 that R_7 is other than hydrogen, especially lower alkoxy,
 lower alkyl, halo, thio lower alkyl or CF_3 . It is most
 10 preferred that the alkyl group alone, or in combination,
 contains 1-2 carbons; and that it is especially most
 preferred that the alkyl group contains 1 carbon atom.
 Preferred R_7 is methyl, ethyl, methoxy, ethoxy, CF_3 or
 thiomethyl. The preferred halo is chloro, bromo and
 15 especially iodo.

Especially preferred compounds of the above
 formulae Ib , Ib_2 , Ib_3 , is Ib_4



or pharmaceutically acceptable salts thereof
 25 wherein R_7 is lower alkyl, halo, thioalkyl, CF_3 and lower
 alkoxy as defined hereinabove.

However in all of the above embodiments, the
 pharmaceutically acceptable salts are the most preferred
 embodiment, especially since the quaternary cations of
 30 Formulae Ib , Ib_2 , Ib_3 and Ib_4 are soluble in aqueous
 solutions.

1 The most preferred quaternary salt is 4-
methyl-3',4',5'-trimethoxybenzylaniline hydrochloride.

It is to be noted that all permutations and combinations of the variables R_1 - R_{19} , Q, X_1 , X_2 , X_3 , Y_1 , Y_2 , Y_3 , T, Z_1 , Z_2 and Z_3 are contemplated by the present invention. Further, it is to be noted that, in addition, Markush groupings containing less than all of the elements described hereinabove as well as the various permutations and combinations thereof are also contemplated by the present invention.

10 Preferred compounds encompassed by Formula I include:

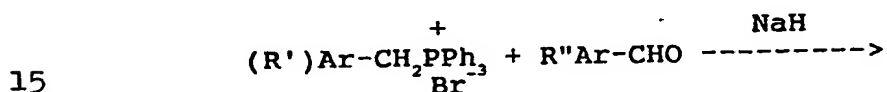
- (Z)-1-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl) ethene;
- (Z)-1-(3-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl) ethene;
- 15 (Z)-1-(2-chloro-4-methoxyphenyl)-2-(2,3,4-trimethoxyphenyl)ethene;
- (Z)-1-phenyl-2-(3,4,5-trimethoxyphenyl)ethene;
- (Z)-1-(4-chlorophenyl)-2-(3,4,5-trimethoxyphenyl)ethene;
- 20 (Z)-1-(4-bromophenyl)-2-(3,4,5-trimethoxyphenyl) ethene;
- (Z)-1-[4-N,N-dimethylamino)phenyl]-2-(3,4,5-trimethoxyphenyl)ethene;
- 25 (E)-1-[4-(N,N-dimethylamino)phenyl]-2-(3,4,5-trimethoxyphenyl)ethene;
- 1-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene;
- 1-[4-(dimethylamino)phenyl]-2-(3,4,5-trimethoxyphenyl)ethene;
- 30 3,4,5-trimethoxy-N-(4-methoxyphenyl) benzyl-

1 amine; and

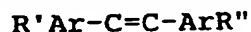
(Z)-1-(4-methylphenyl)-2-(3,4,5-trimethoxy-phenyl)ethene.

5 A most preferred compound of Formula I is (Z)-1-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene.

The compounds of the present invention can be prepared by art-recognized techniques. Although the examples described hereinbelow may be specific, the syntheses are general. For example, in the Wittig reaction described hereinbelow and depicted in Scheme 1, 10 a heteroaryl-arorylmethylene-triphenylphosphonium can in reaction with a heteroaryl or aryl aldehyde under Wittig-like conditions



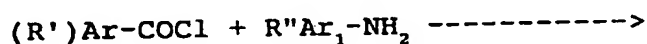
to form the corresponding



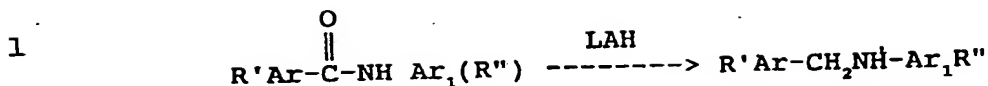
20 Further hydrogenation of the stilbene gives the corresponding dihydro stilbenes. In the scheme, Ar, Ar₁, R' and R'' are defined herein.

Similarly, the formation of the compound of Formula Ia wherein X is CONH or CH₂NH depicted in Scheme 6 is also general and is applicable to compounds of Formula Ia when Ar and Ar₁ are other than phenyl. For 25 example, the reaction in Scheme 6 is general for the reaction between an aryl or heteroaryl acid chloride and an aryl or heteroaryl amino reacted under amide forming condition followed by reduction with LiAlH₄, as shown hereinbelow:

30



35



5 Similarly, the reactions in Scheme II-V + VII-XIII are general and can be depicted to encompass the syntheses of compounds when Ar and Ar₁ are as defined herein. Therefore, the syntheses described in those enumerated schemes are to read in that light.

10 Chemistry

Wittig reaction of phosphonium bromide compounds 3a-b with aryl aldehyde compounds 4a-4n in THF in the presence of sodium hydride followed by preparative thin layer chromatographic separation gave the corresponding cis stilbene compounds 5a-n and trans stilbene compounds 6a-6n (Reaction Scheme I; see Table I). In general all these reactions gave the cis isomers as major components, and, except in a few cases, trans isomers were also isolated as minor products in yields of over 10%. However, in the case of aryl aldehydes with a substituent at the 2-position (compounds 4c, 4d and 4e) and pyridine-2-carboxaldehyde, cis isomers were obtained in very high yields, and the trans isomers were obtained in poor yields. With 2,3,4-trimethoxybenzaldehyde compound (4d) an isolable amount of the trans stilbene was not obtained. Trans-stilbene compounds 6q-6y were prepared by the Wittig-Horner reaction of phosphonate ester compounds 7a-c with the aryl aldehydes 4d and 4o-4t in DMF using sodium methoxide as the base (Scheme II). Under these reaction conditions, trans isomers were obtained exclusively. 4-Hydroxystilbene compounds 5o and 6o were prepared from

1 the corresponding O-silyloxyated stilbenes 5m and 6m by
the action of tetra-n-butylammonium fluoride in THF. In
another set of reactions, the 4'-acetoxystilbenes 5p and
6p were prepared by acetylation of 4'-hydroxystilbenes
5o and 6o (Scheme III). Cis or trans geometries of most
5 of these compounds were confirmed by their
characteristic coupling constants for the olefinic
protons of about 12 Hz for cis and 16.0-16.5 Hz for
trans isomers. The two olefinic protons of compounds
10 5d, 5m, 6g and 6p gave singlets and those of compounds
5o and 6b gave multiplets, and the geometries of these
compounds were assigned relative to their isomers, which
gave distinct doublets with characteristic coupling
constants. Catalytic hydrogenation of E-stilbene
15 compounds 6 at about 40 psi in the presence of 10%
palladium on charcoal gave dihydrostilbene compounds 8
(Scheme IV). Lithium aluminum hydride reduction of (E)-
4'-nitro-3,4,5-trimethoxystilbene (6l) provided (E)-4'-
amino-3,4,5-trimethoxystilbene (6z). Catalytic
hydrogenation of compound 6l in EtOAc at 40 psi in the
20 presence of 10% palladium on charcoal gave 4'-amino-
3,4,5-trimethoxydihydrostilbene (8z), which on
subsequent reaction with acetyl chloride gave the
acetamido compound 8m (Scheme V). Scheme VI describes
the general method adopted for the preparation of amide
25 compounds 11a-11f and their subsequent reduction to
substituted benzylamines 12a-12f.

4-Benzyloxy-3,5-dimethoxybenzaldehyde (13j)
was prepared by the reaction of syringaldehyde with
benzyl chloride in the presence of K_2CO_3 in boiling
30 acetone. Similarly, reaction of t-butyldimethylsilyl
chloride with syringaldehyde in DMF in the presence of

1 N,N-diisopropylethylamine gave 4-(t-butyldimethyl-
silyl)-oxy-3,5-dimethoxybenzaldehyde (13k) (Scheme VII).
Wittig reaction of phosphonium bromides 14a-b with
benzaldehydes 13a-k in THF in the presence of sodium
5 hydride followed by preparative thin-layer
chromatographic separation of the crude products
afforded the cis stilbenes 15a-k and trans stilbenex
16a-k (Scheme VIII). Reaction of compounds 15k and 16k
with tetra-n-butylammonium fluoride and in situ
10 acetylation of the phenols with acetic anhydride gave
the acetoxy compounds 15l and 16l (Scheme IX). The cis
and trans geometries of the stilbenes were assigned by
the characteristic ¹H NMR coupling constants of the
olefinic protons. Catalytic hydrogenation of stilbenes
15 and 16 at about 40 psi in the presence of 10%
15 palladium on charcoal gave the dihydrostilbenes 17a-e
(Scheme XIII). The amino ethers 17f-g were prepared by
the reaction of 1-(4-hydroxyphenyl)-2-(3,4,5-
trimethoxyphenyl)ethane (18) with dialkylaminoethyl
chlorides 19a-b in refluxing acetone in the presence of
20 K₂CO₃ (Scheme X). Compounds 17h and 17i were prepared by
the alkylation of 3,4,5-trimethoxyphenyl-acetonitrile
(20a) and 4-methoxyphenylacetonitrile (20b) with 4-
methoxybenzyl bromide (21a) and 3,4,5-trimethoxybenzyl
bromide (21b), respectively, using LDA as the base
25 (Scheme XI). Similarly, alkylation of methyl 4-
methoxyphenylacetate (20b) with 3,4,5-trimethoxybenzyl
bromide 21b gave product 17j.

Several derivatives containing acidic and
basic functional groups, including the previously
30 mentioned amines 17f-g, were prepared in an attempt to
make compounds that were more soluble in water and could

1 therefore be formulated more easily. Base catalyzed
condensation of phenylacetic acids 22a-b with aryl
aldehydes 13l-n in the presence of triethylamine gave
the carboxylic acids 23a-c (Scheme XII). Esterification
5 of compounds 23a-b with methanol using a catalytic
amount of H_2SO_4 gave products 24a-b (Scheme XII).
Reaction of thionyl chloride with the carboxylic acids
23a-b in refluxing benzene gave the corresponding acid
chlorides, which on subsequent reaction with appropriate
10 amines and alkylaminoalcohol gave compounds 24c-f
(Scheme XII).

The effect of shortening the distance between
the two aromatic rings was investigated by preparing
compound 29, having a methylene unit separating the
rings. Friedel-Crafts acylation of anisole with 3,4,5-
15 trimethoxybenzoyl chloride gave 3,4,4',5-
tetraethoxybenzophenone (27, Scheme XIII). Sodium
borohydride reduction of compound 27 in methanol
afforded 4-methoxy-phenyl-(3,4,5-trimethoxyphenyl)-
methanol (28), which on catalytic hydrogenolysis in the
20 presence of 10% palladium on charcoal gave 4-methoxy-
phenyl-(3,4,5-trimethoxyphenyl)methane (29) (Scheme
XIII).

Several conformationally rigid analogues of
the compound 5a were synthesized in an attempt to gain
25 evidence concerning the biologically active conformation
of this substance. Different conformations are
available to 5a through rotation about the two bonds
connecting the aromatic rings to the alkene unit. This
question was investigated by forming a covalent bond
30 between the two aromatic rings of several stilbenes,
resulting in the phenanthrenes 32a-d (Scheme XIV).

1 Photocyclization of the cis-trans mixtures of stilbenes
30a-c and 31a-c in the presence of iodine afforded the
desired phenanthrenes 32a-d. Conformationally
restricted analogues of the active dihydrostilbene 8a
were also prepared. Synthesis of one such compound
5 based on the indane system is detailed in Scheme XV.
Hydrolysis of the methyl ester 17j under basic
conditions gave the acid 33. The indanone 34 was then
prepared by an intra-molecular Friedel-Crafts acylation
reaction using the acid chloride derived from 33. The
10 desired indane 35 was obtained by treatment of 34 with
hydrogen in the presence of palladium on charcoal.
Several conformationally restricted congeners of the
dihydrostilbene 8a were prepared based on the 1-
benzylisoquinoline ring system. In these compounds, the
15 rotation about the trimethoxybenzene ring and the
attached carbon of the stilbene moiety is restricted.
Compounds 36, 37, 38, and 41 (Scheme XVI) are known
compounds that resynthesized by a modification of the
route originally published by Kupchan et al. Treatment
20 of 36 with DDQ gave derivative 39, which was methylated
using methyl iodine to afford compound 40.

A conformationally rigid
tetrahydroprotoberberine analogue of 8a was also
synthesized as shown in Scheme (XVII). Acylation of the
25 primary amino group of 42 with acetyl chloride gave the
acetamide derivative 43. A Bischler-Napieralski
reaction involving the treatment of 43 with phosphorus
oxychloride afforded the dihydroisoquinoline 44.
Reaction of 44 with the acid chloride 45 yielded 46,
30 which underwent the enamide photocyclization reaction to
give the substituted protoberberine 47. Reduction of 47

1 by sequential treatment with lithium aluminum hydride
and sodium borohydride yielded the desired
tetrahydroprotoberberine 48. In this compound, each of
the three C-C bonds connecting the two aromatic rings of
5 the 1,2-diphenylmethane moiety is conformationally
restricted.

10

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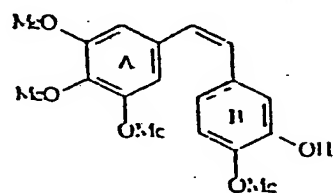
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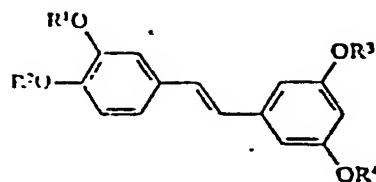
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1 Prior Art Structures

5



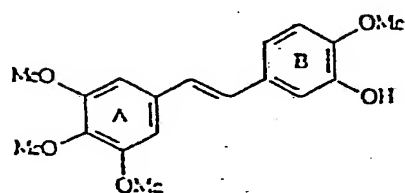
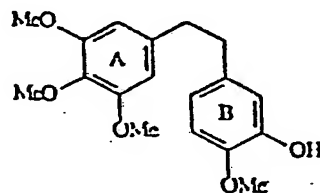
Combretastatin A-4 (1a)

 $R^1=R^2=R^3=R^4=H$ Piccattanol (2a)

10

 $R^1=Me; R^2=R^3=R^4=H$ 3,3',5'-Tri-*O*-methylpiccattanol (2b) $R^2=Me; R^1=R^3=R^4=H$ 4,3',5'-Tri-*O*-methylpiccattanol (2c)

15

*trans*-Combretastatin A-4 (1b)

Dihydrocombretastatin A-4 (1c)

20

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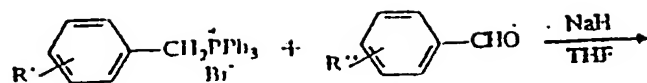
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1 Schemes

5

Scheme 1



3a-l

4a-n

10

R'

3a: 3,4,5-(OMe)₃

3b: 4-OMe

R''

4a: 4-OMe

4b: 3-OMe

4c: 2-OMe

4d: 2,3,4-(OMe)₃

4e: 2-Cl-4-OMe

R''

4g: 4-Cl

4h: 4-Br

4i: 4-NO₂

4m: 4-OSi(t-Bu)Me₂

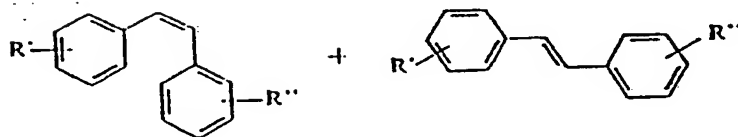
4n: 3-OMe

15

4f: H

4i: R''-C₆H₄ = 4-pyridyl4j: R''-C₆H₄ = 3-pyridyl4k: R''-C₆H₄ = 2-pyridyl

20



5a-n

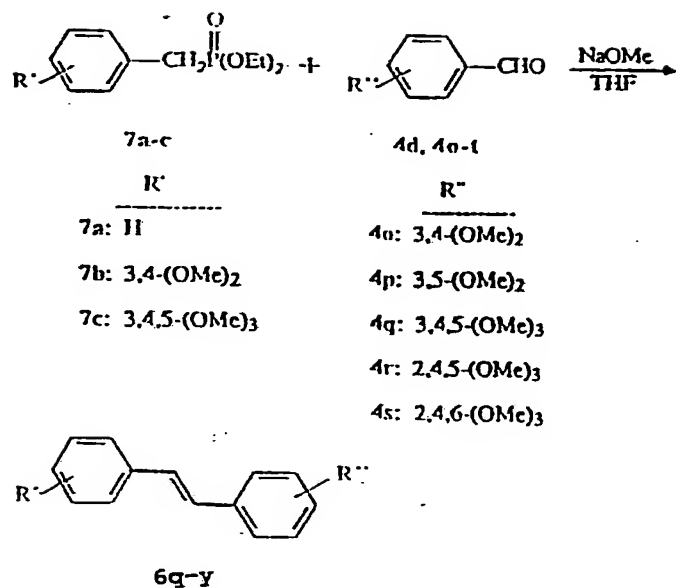
6a-n

25

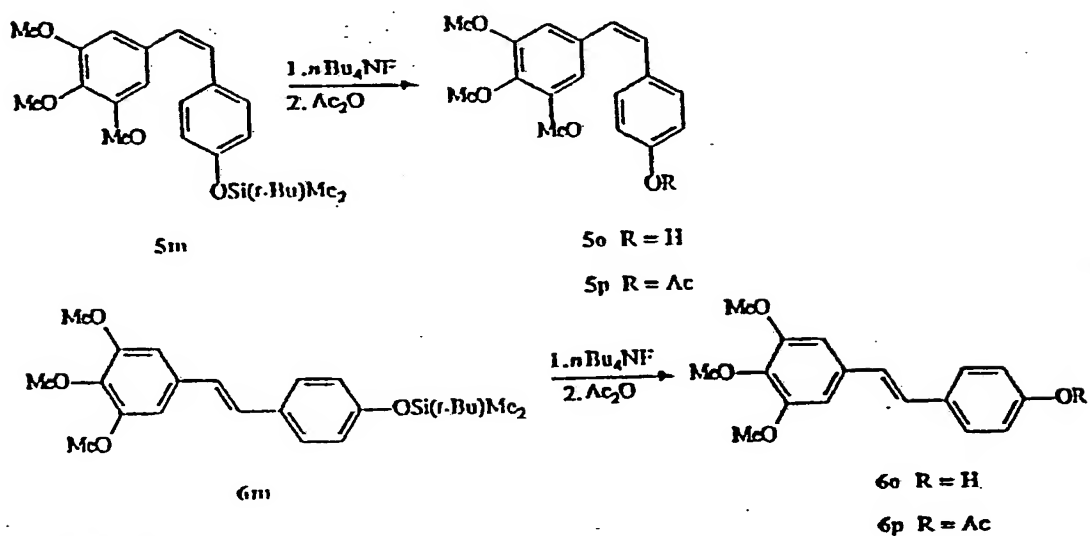
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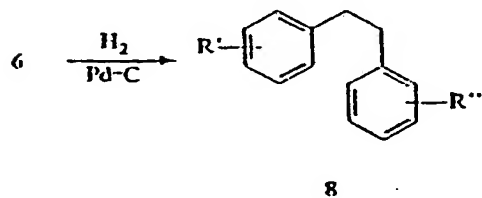
Scheme II



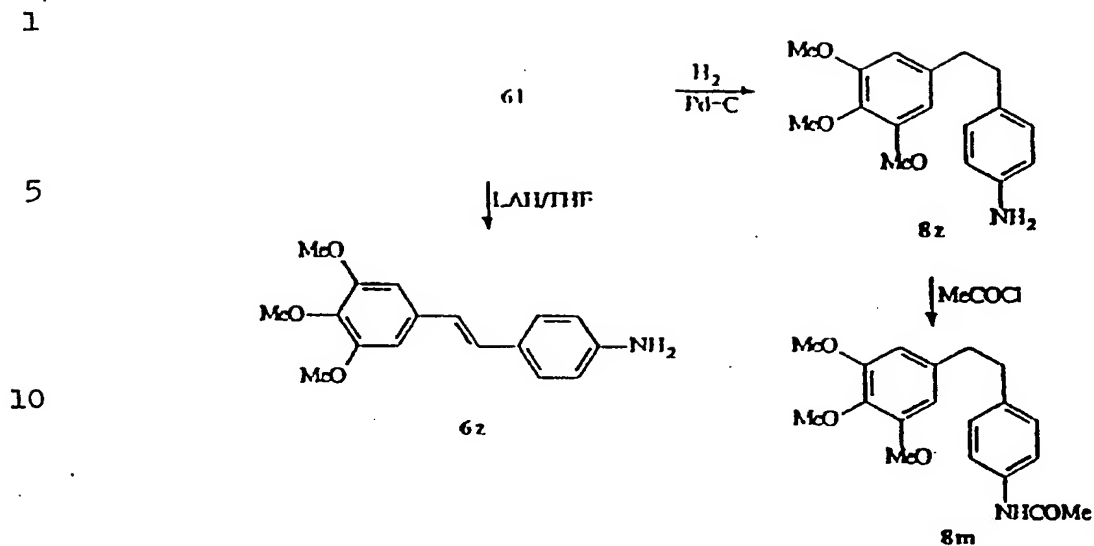
Scheme III



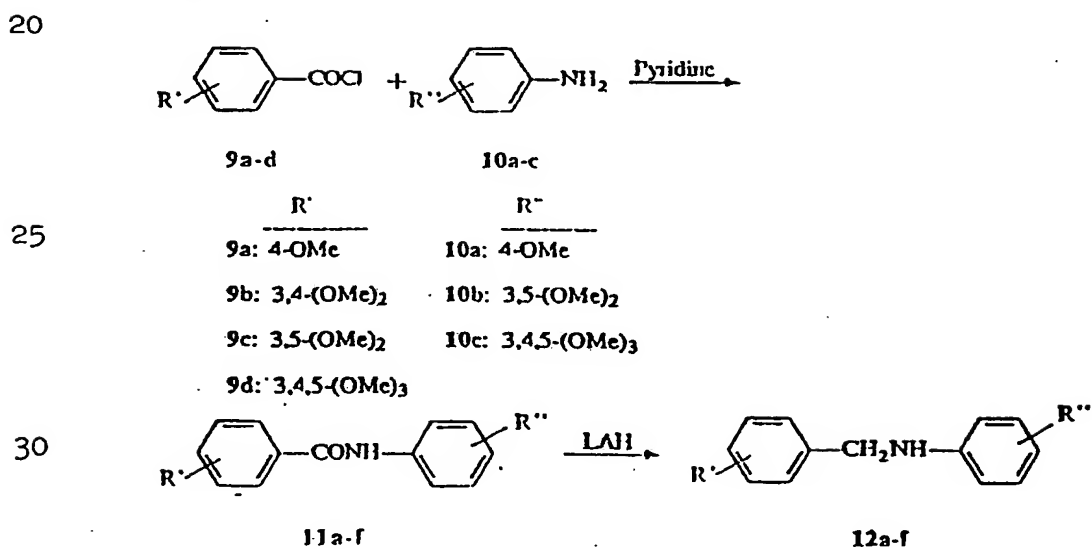
Scheme IV



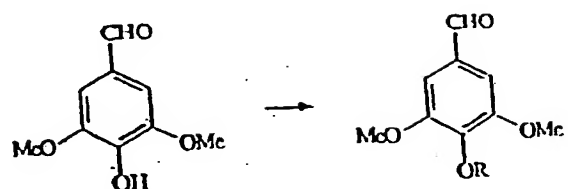
Scheme V



Scheme VI



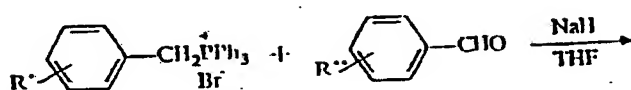
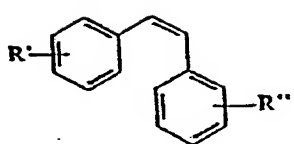
Scheme VII



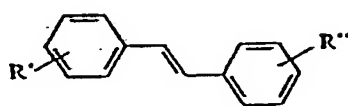
13j: R=Bn

13k: R=Si(t-Bu)Me₂

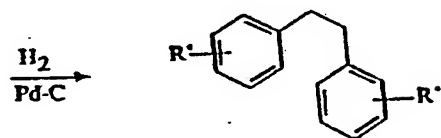
Scheme VIII

14a-b
R'13a-k
R''5a: 3,4,5-(OMe)₃
5b: 4-OMe13a: 4-OEt
13b: 4-O-n-Pr
13c: 4-SMe
13d: 4-Me
13e: 4-Et13g: 4-t-Bu
13h: 3,4-(OMe)₂
13i: 3,5-(OMe)₂
13j: 3,5-(OMe)₂-4-OBn
13k: 3,5-(OMe)₂-4-OSi-
t-BuMe₂

15a-b



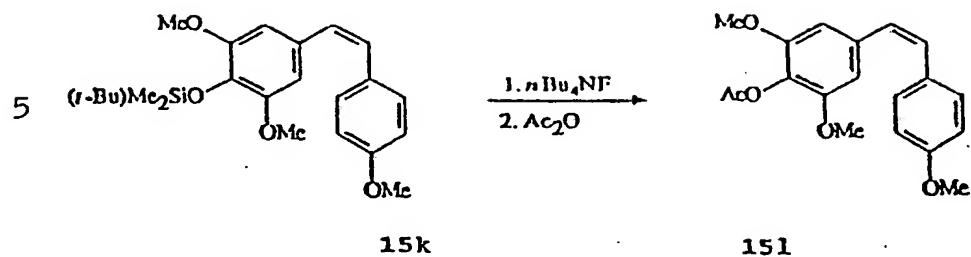
16a-b



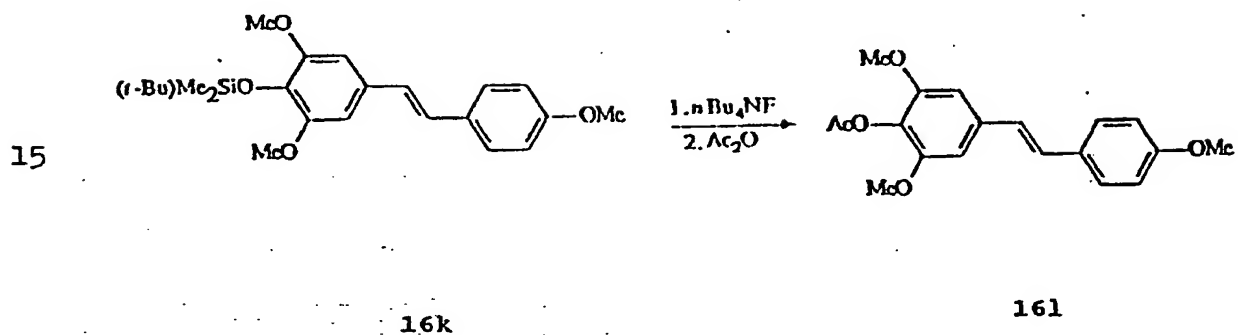
17a-e

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Scheme IX

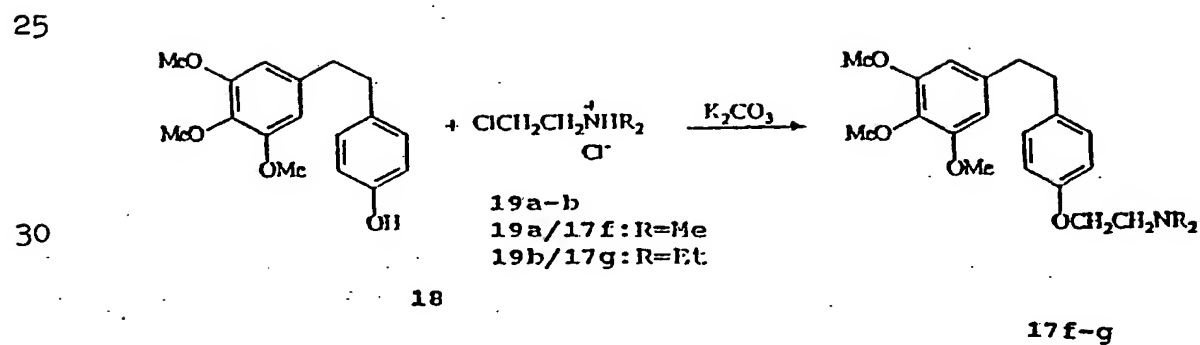


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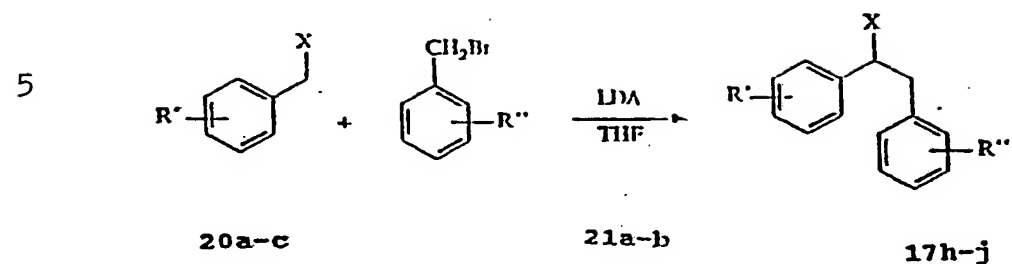


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Scheme X



1 Scheme XI

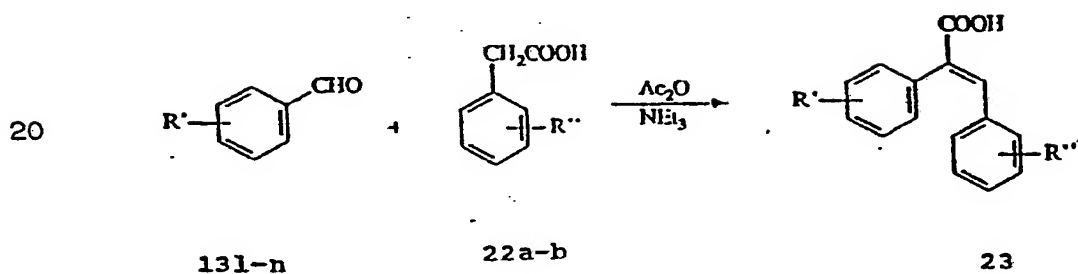


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20a: R' = 3,4,5-(OMe)₃, X = CN
 20b: R' = 4-OMe, X = COOMe
 21a: R'' = 4-OMe
 21b: R'' = 3,4,5-(OMe)₃

15

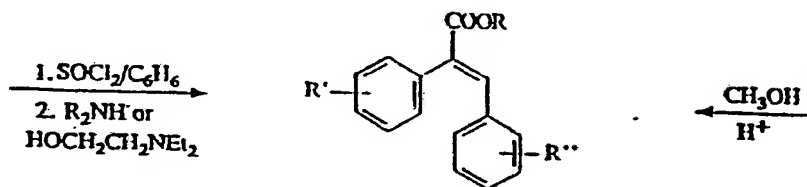
Scheme XII



25

13l: 4-OMe
 13m: 3-OMe
 13n: 3,4,5-(OMe)₃
 22a: 3,4,5-(OMe)₃
 22b: 4-OMe

30



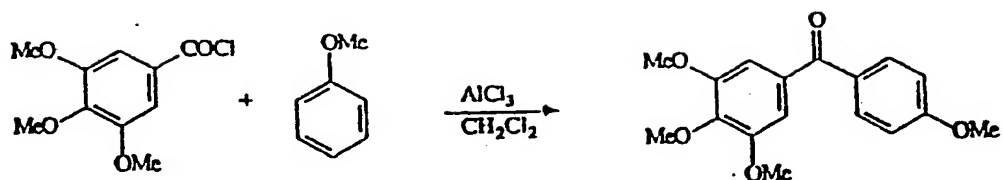
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-31-

Scheme XIII

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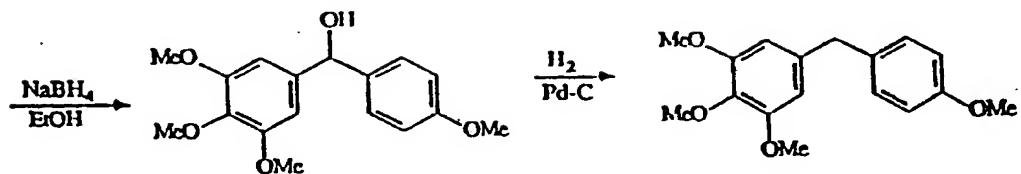


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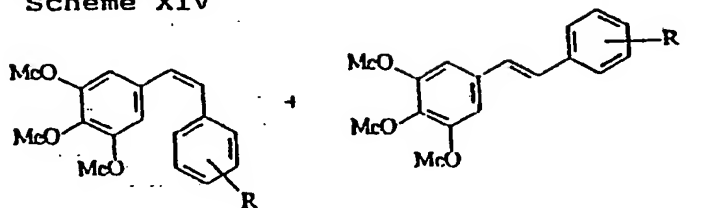
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Scheme XIV

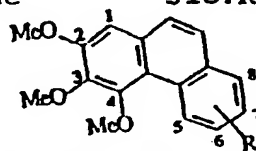
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30a: R=3'-OMe
 30b: R=4'-OMe
 30c: R=2'-OMe

31a: R=3'-OMe
 31b: R=4'-OMe
 31c: R=2'-OMe

30

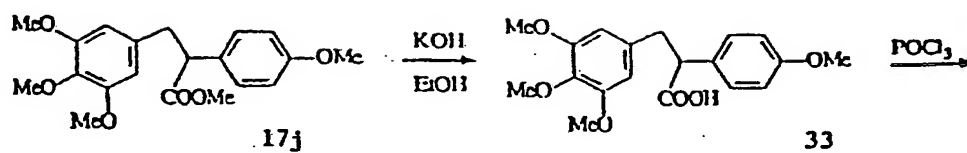


32a: R=5-OMe
 32b: R=6-OMe
 32c: R=7-OMe
 32d: R=8-OMe

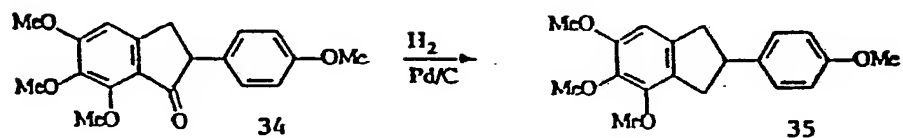
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Scheme XV

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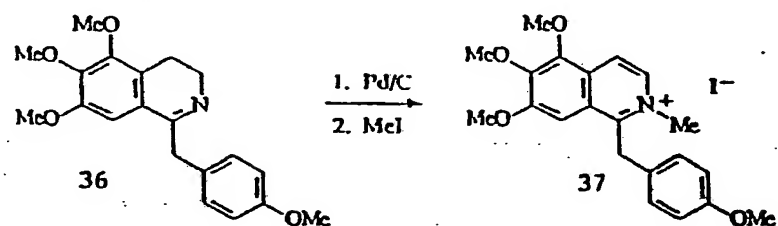
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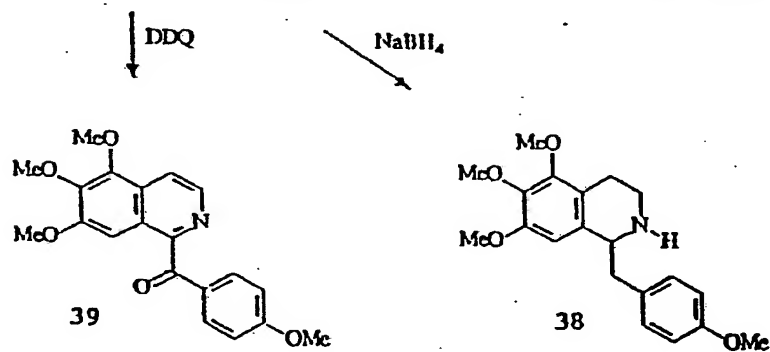
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Scheme XVI

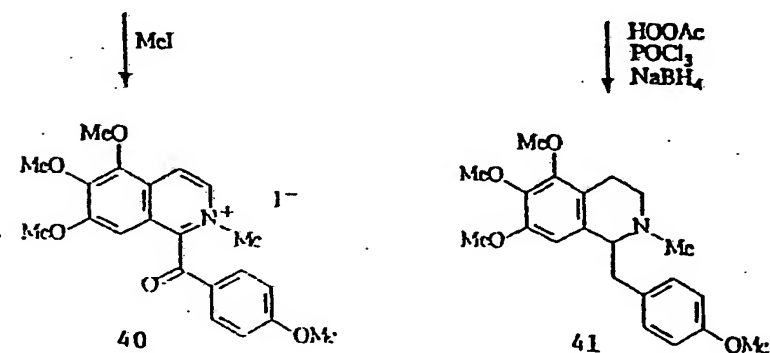
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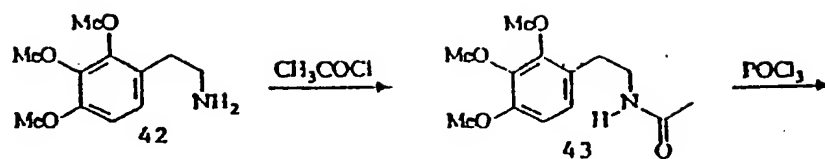
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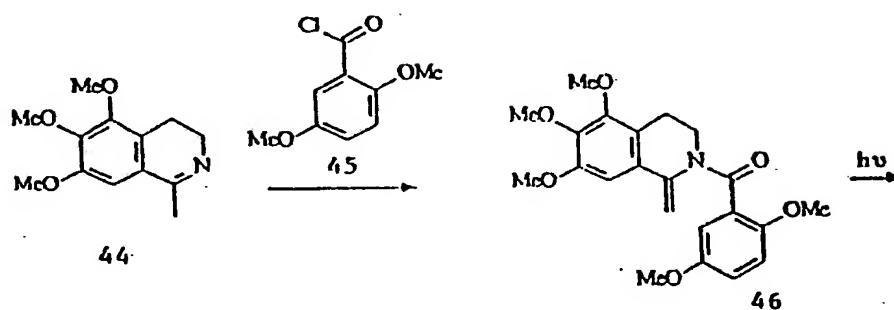
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Scheme XVII

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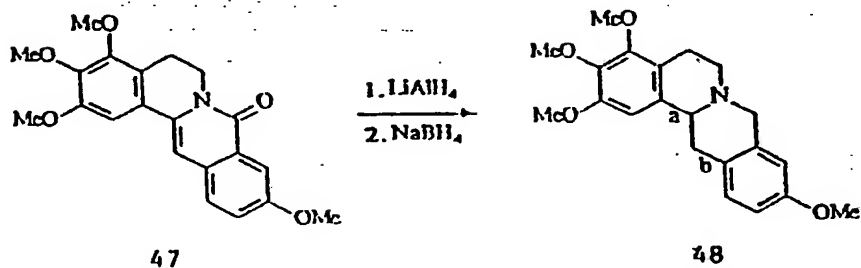


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1 Compounds of the present invention exhibit
tubulin polymerization inhibitory activity. They also
display anti-tumor, especially anti-cancer activity, and
thus, are anti-cancer agents, useful for the treatment
of cancer, as shown by the assays described hereinbelow.

5 Pharmacological Testing

A wide variety of compounds encompassed by
Formula I were synthesized and tested against five
cancer cell cultures: A-549 lung carcinoma, MCF-7 breast
carcinoma, HT-29 colon adenocarcinoma, SKMEL-5 melanoma
and MLM melanoma. Pharmacological test results are
summarized in Tables I-IX. Pharmacological testing
procedures utilized were as follows.

Cytotoxicity Assays

15 An MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-
diphenyl-tetrazolium) calorimetric assay was employed
according to the established procedure of Alley, et al.,
Cancer Research, 48, February 1, 1988, pgs. 589-601; and
Mosmann, T., J. Immunol. Meth., 65, (1983), pgs. 55-63.
The description of these assays described therein are
20 incorporated herein by reference. After the addition of
the samples to the cell cultures, the cells were
incubated for six days before the MTT reagent was added.
The assays were performed at Purdue Cell Culture
Laboratory. All of the compounds were initially tested
25 once for each of the cell lines listed in Tables I-IV.
The active compounds ($ED_{50} < 25 \mu M$) were tested again,
and the values shown for these cytotoxic substances are
the averages of two determinations.

30

35

1 Tubulin Polymerization and Colchicine Binding Assays

Electrophoretically homogeneous tubulin was purified from bovine brain as described previously by Hamel et al., Biochemistry, 23, (1984), pg. 4173.

5 Determination of IC_{50} values for the polymerization of purified tubulin was performed as described in detail by Muzaffar et al., J. Med. Chem., 33, (1990), pgs. 567-571, the pertinent contents of which are incorporated herein by reference. In brief, tubulin was preincubated

10 at 37°C with varying compound concentrations, reaction mixtures were chilled on ice, GTP (required for the polymerization reaction) was added, and polymerization was followed at 37°C by turbidimetry at 350 nm in Gilford recording spectrophotometers equipped with

15 electronic temperature controllers. Four instruments were used, and two control reaction mixtures were present in each experiment. The extent of polymerization after a 20 min incubation was determined (the values for the two controls were usually within 5% of each other). IC_{50} values were determined graphically.

20 Active compounds were examined in at least three independent assays, while inactive compounds (defined as IC_{50} value > 50 μ m) were examined in at least two independent experiments. (It is to be noted that the term "inactive", as used herein does not mean that a

25 given compound has no activity. As used herein, the term means that it has activity, but its IC_{50} value in a particular assay is > 50 μ m.) The effect of agents on the binding of [3 H]colchicine (obtained from Amersham) to tubulin was measured by the DEAE-filter technique.

30 Among the first group of compounds tested (i.e., 4a to 12f), eleven of them, 5a, 5b, 5e-h, 5n, 6n,

1 8a, 8n, and 12a were found to have significant
cytotoxicity ($ED_{50} < 1 \mu M$ in at least three cell lines).
In general, cis stilbenes were more potent than the
other groups of compounds, and (Z)-1-(4-methoxyphenyl)-
2-(3,4,5-trimethoxyphenyl)ethene (5a) was the most
5 potent of all. Taking compound 5a as the model compound
for a structure-activity relationship discussion, the
presence of a 4-methoxy group in the B-ring plays a very
important role for this compound to be highly cytotoxic.
Transfer of the 4-methoxy group in the B-ring to the 3-
10 or 2-position (compounds 5b and 5c) or substitution of
it with H, NO_2 , $OSi(t-Bu)Me_2$, OH, OAc (compounds 5f, 5l,
5m, 5o and 5p) decreased the activity drastically.
Similarly, introduction of a Cl group at the 2-position
of 5a (compound 5e) decreased the cytotoxicity.
15 However, when the methoxy group in the B-ring was
substituted with a Cl, Br, or NMe_2 group (compounds 5g,
5h, 5n), although the potency decreased they were still
highly cytotoxic ($ED_{50} < 10^{-1} \mu M$). Rotating the three A-
ring methoxy groups from the 3,4,5-positions to the
20 2,3,4-positions reduced the cytotoxicity by more than
five orders of magnitude. In another modification we
replaced the B-ring of compound 5a with 4-, 3-, or 2-
pyridyl rings (compounds 5i, 5j, 5k) and none of them
were active ($ED_{50} > 10 \mu M$). These results show that the
25 exact locations of the four methoxy groups are very
important features for the pronounced cytotoxicity of
compound 5a and that changes in their locations result
in decreased potency. In comparison with combretastatin
A-4 (1a), compound 5a was found to be approximately 140
30 times more cytotoxic against HT-29 cells and about 10
times more cytotoxic against MCF-7 cells than

1 combretastatin A-4 (1a). However, 5a was found to be
about 20 times less cytotoxic against A-549 cells, 30
times less cytotoxic against SKMEL-5, and 7 times less
cytotoxic against MLM cells than combretastatin A-4
5 (1a).

Except for compound 6n, trans-stilbenes had
lower activity. This includes tetramethylated
piceatannol (6y), and its methoxylated derivatives 6s,
6t, 6u and 6v. Only two dihydrostilbenes (compounds 8a
10 and 8n) were found to be highly active, with 8a being
the second most cytotoxic agent prepared (ED_{50} values
about $2 \times 10^{-4} \mu M$). Compound 8a was more cytotoxic than
dihydrocombretastatin A-4 (1c) in all five cancer cell
lines studied here. When the ethylene bridge in
15 compound 8a was replaced with an amide or an
aminomethylene linkage (compounds 11a, 11c, 12a, 12c and
other analogues), none of the amides had significant
activity ($ED_{50} > 1 \mu M$), but the N-benzylamine derivative
12a possessing the closest structural analogy to 8a was
20 active. 3,4,5-Trimethoxy-N-(4-methoxyphenyl)benzylamine
(12a) was only an order of magnitude less cytotoxic than
8a (ED_{50} in the $10^{-3} \mu M$ range).

The mechanism of action of the combretastatins
has been shown to be at the microtubule level, since
they cause cells to accumulate in apparent metaphase
25 arrest and inhibit in vitro microtubule assembly. They
bind specifically to tubulin, the major component of
microtubules, at the colchicine binding site, since
combretastatin A-4 (1a) has been shown to competitively
inhibit the binding of radiolabeled colchicine to
30 tubulin.

1 Initial investigation of several of the
synthetic compounds prepared here revealed that they do
in fact cause mitotic arrest in cell culture. A
detailed quantitative study of the effects of most of
5 these substances on tubulin polymerization was therefore
performed. With the exception of compounds 5p and 12d,
noncytotoxic agents had minimal effects on
polymerization (IC_{50} values $> 50 \mu M$), but significant
inhibition of the reaction occurred with ten of the
10 eleven highly cytotoxic compounds and with compounds 5p
and 12d. Tubulin polymerization and colchicine binding
inhibition data of the compounds encompassed hereby were
compared with simultaneously obtained inhibitory data
for the effects of combretastatin A-4 (1a; cf. 5a), its
15 trans isomer (1b; cf. 6a), and its dihydro derivative
(1c; cf. 8a) (Table VIII). Data are presented as well
for podophyllotoxin, a potent tubulin inhibitor which
binds at the colchicine site, and for thiocolchicine, a
particularly potent colchicinoid which has reproducibly
yielded the lowest IC_{50} value in the polymerization assay
20 for agents binding to the colchicine binding site.

Compound 5a is a most potent new agent as an
inhibitor of tubulin polymerization, with an IC_{50} value
($2.2 \mu M$) essentially indistinguishable from those of
combretastatin A-4 and podophyllotoxin and somewhat
25 higher than that of thiocolchicine. This is in
agreement both with compound 5a possessing one of the
highest cytotoxicity of the new compounds and with its
close similarity to combretastatin A-4 (1a) in its
overall effects on the cell lines evaluated. The
30 difference in IC_{50} values between the two dihydrostilbene
compounds 1c and 8a was more noticeable. The

1 combretastatin A-4 analog 1c had an IC_{50} value of 3.3 μM ,
only modestly lower than the IC_{50} value of combretastatin
A-4, but the corresponding hydrogenation of compound 5a
to yield compound 8a resulted in an almost 4-fold
5 increase in the IC_{50} value, from 2.2 to 7.9 μM .
Similarly, the modest reduction in activity in the cis
stilbene 5n as compared to combretastatin A-4 (1a) (3.5
versus 1.9 μM) was not reflected in the dihydrostilbene
analog 8n, which had an IC_{50} value of 29 μM . Cis
10 stilbene compounds 5b, 5e, 5g, and 5h were also active
as inhibitors of tubulin polymerization, while the
remaining ten cis stilbenes had less activity. It
should be noted that, with the exception of the most
potent agents (1a and 5a), there was only qualitative
15 agreement between the tubulin polymerization and cell
culture assays. For example, while
dihydrocombretastatin A-4 (compound 1c) was more
effective than compound 8a as an inhibitor of tubulin
polymerization, the latter agent was more cytotoxic with
the cell lines studied here. Similarly, although the
20 halogenated cis stilbenes 5e, 5g and 5h were not much
less active than 1a and 5a as inhibitors of tubulin
polymerization, they were about 1000-fold less
cytotoxic.

25 The cytotoxic compounds gave reproducible
results in the tubulin polymerization assay with the
exception of the trans stilbenes 1b and 6n. Initial
evaluation of these compounds in the tubulin
polymerization assay yielded results concordant with the
cytotoxicity data, although the apparent IC_{50} value
30 obtained in the polymerization assay for 6n was
difficult to reproduce and that for 1b initially

1 obtained in the current experiments was lower than that
obtained previously. It was found that both 1b and 6n
solutions increased in activity with storage, and that,
when care was taken to evaluate the solutions
5 immediately after their preparation, neither trans
stilbene was able to significantly inhibit tubulin
polymerization. This suggested that both compounds were
unstable in solution, and that more active agents might
be formed during their storage. The cytotoxic
10 properties of these two agents may similarly result from
chemical changes in solution. 500 MHz NMR analysis of
6n in solution demonstrated significant formation of the
cis isomer 5n. The ratio of 6n:5n was 1:1 after 24
hours of the dissolution of pure 6n in DMSO at room
15 temperature. In a separate analysis of the stability of
compound 1b in DMSO at room temperature (well protected
from light), ¹H NMR analysis over a period of one month
at frequent intervals confirmed the formation of about
3% and 10% of the cis isomer (compound 1a) after two and
four weeks, respectively.

20 Compounds 5a and 8a can be taken as standards
for structure activity comparisons of cis stilbenes and
dihydrostilbenes, respectively, in the tubulin
polymerization assay. Without exception, when the same
modified analog was available in both series, a greater
25 loss of activity occurred in the dihydrostilbene than in
the analogous cis stilbene (cf. 5b and 6b; 5f and 6f; 5n
and 6n; 5p and 6p).

In the cis stilbene series, a shift of a
single methoxy group in the A ring, from position 5 to
30 position 2, yielded an inactive agent (5d). When the B
ring methoxy group was shifted from position 4' to

1 position 3', there was a 4-fold drop in activity
(compound 5b; IC_{50} , 8.8 μ M). When the B ring methoxy
group was eliminated, there was a much larger drop in
activity (compound 5f; IC_{50} , 36 μ M), while its placement
5 at the 2' position yielded the compound 5c, which
exhibited low activity. Addition of a Cl at position 2'
(compound 5e) or replacement of the methoxy group with a
Cl (5g), Br (5h), or NMe_2 (5n) group resulted in small
reductions in antitubulin activity. Demethylation of
10 the 4'-methoxy group led to compound 5o, and its
replacement with an acetyloxy group yielded a weak
inhibitor (compound 5p; IC_{50} , 29 μ M).

Turning to the dihydrostilbene series,
replacement of the B ring methoxy group with an amino
group (compound 8z) resulted in lower activity, but
15 activity was increased if the amino group was converted
to a dimethylamino group (compound 8n; cf. 5n).
Addition of one (compound 8s) or two (compounds 8t-8v)
additional methoxy groups to the B ring also resulted in
lower activity. An enhancement of antitubulin activity
20 in the 5a/8a structure was obtained by modification of
the substituents on the B-phenyl ring by the addition of
a single hydroxy group at position 3' (as occurs in
combretastatin A-4 (1a) and dihydrocombretastatin A-4
(1c)) or addition of two hydroxy groups in a vicinal
25 diol arrangement at positions 2' and 3' (as occurs in
combretastatin A-1 and B-1).

Replacement of the ethylene bridge connecting
the two aromatic rings in compound 8a with amide or
aminomethylene units as represented by compounds 11a,
30 11d and 12c resulted in lower inhibitory activity in the
tubulin polymerization assay. On the other hand,

1 replacement of the ethylene bridge of 8a with an
aminomethylene unit with the alternative orientation
shown in compound 12a resulted in only a 3-fold loss of
activity (increase in the IC_{50} value from 7.9 μM for
5 compound 8a to 23 μM for compound 12a). Comparing
compound 12a to compound 12d indicates that only a small
loss of activity occurs with elimination of the 4-
methoxy group of the A ring (IC_{50} of 29 μM without the
methoxy group as opposed to 23 μM). However, the
10 presence of a 4-methoxy group on the aniline partition
of the benzyanilines increases activity.

Combretastatin A-4 (1a) and compound 1c
inhibit the binding of radiolabeled colchicine to
tubulin. Therefore Formula I compounds were evaluated
15 in this assay too. The Formula I compounds relative
activity as inhibitors of colchicine binding correlated
well with their activity as inhibitors of tubulin
polymerization. The mechanism of action of the new
compounds, like that of the combretastatins, thus
20 appears to involve an interaction of the drug with the
colchicine binding site of tubulin. Only compound 5a,
however, approached the nearly total inhibition of
colchicine binding observed with equimolar
combretastatin A-4 (1a).

25 With the compounds described here, as with the
combretastatins and other classes of antimitotic agents,
there is only partial agreement between cytotoxicity and
effects on tubulin, the presumptive target molecule.
Seven of the most cytotoxic agents (compounds 5a, 5b,
5e, 5g, 5h, 5n and 8a) were strong inhibitors of tubulin
30 polymerization, and, except for the trans-stilbene 6n,
no compound indicated to be inactive, as defined herein,

1 as an inhibitor of tubulin polymerization had
significant cytotoxic activity. Nevertheless, compounds
8n and 12a were strongly cytotoxic yet had only modest
inhibitory effects on tubulin polymerization.
5 Similarly, the structural differences between compounds
12a and 12d yielded only minor differences in
antitubulin activity but resulted in major changes in
their cytotoxic properties.

Besides the clear analogy of the compounds
described here to the combretastatins, the activity
10 observed in compound 5n, and to a lesser extent in
compound 8n, suggests a relationship to the
benzylbenzodioxole class of agents synthesized by Jurd.
(See Jurd et al., J. Agric. Food Chem., 27, 1979, pg.
1007-1016 and Jurd, L., J. Heterocycl. Chem. 22, 1985,
15 pg. 993.) Among the active tubulin inhibitors were
compounds 13, 14 and 15 with the latter having the
dimethylamino substituent in common with 5n.

The relative potencies 5a > 8a > 6a for these
cis, dihydro, and trans compounds as inhibitors of
20 tubulin polymerization are in agreement with the
relative potencies previously observed for
combretastatin A-4 (1a) and dihydrocombretastatin A-4
(1c) and our finding herein that freshly dissolved
trans-combretastatin A-4 (1b) has some activity.
25 Without wishing to be bound, it is assumed that the
flexibility of the dihydro compound 8a allows it to
adopt a conformation resembling the cis isomer 5a, which
explains why compound 8a is more cytotoxic and potent as
a tubulin polymerization inhibitor than the trans isomer
30 compound 6a. The relative potencies 5a > 8a > 6a for
these cis, dihydro, and trans compounds, respectively,

1 as inhibitors of tubulin polymerization were also
reflected in the results of the cytotoxicity assays.
These relative potencies of 5a > 8a > 6a in the
cytotoxicity assays are also in agreement with the
5 relative cytotoxicities of 1a > 1c previously reported
for L1210 murine leukemia cells in the combretastatin
series, although in that study 1b was intermediate in
cytotoxic activity between 1a and 1c.

As mentioned above, modifications were
performed on (Z)-1-(4-methoxyphenyl)-2-(3,4,5-
10 trimethoxyphenyl)ethene (5a) by rotating the four
methoxy groups of both A- and B-rings to different
positions and it was established that their locations as
in compound 5a were essential for the pronounced
cytotoxicity and antitubulin activity of 5a. As an
15 extension of that investigation, additional cis stilbene
derivatives were synthesized in which the 5-OMe or 4-OMe
substituents were removed (compounds 15h and 15i,
respectively) and these changes resulted in complete
loss (15h:ED₅₀ > 25 μ M in all cell lines) or significant
20 reduction (15i:ED₅₀ in the 10⁻¹ μ M range) of the
cytotoxicity. It is noteworthy that the ability of 15i
to inhibit tubulin polymerization (IC₅₀ 3.8 μ M) is not
greatly reduced relative to that of 5a (IC₅₀ 2.5 μ M),
while that of 15h (IC₅₀ 18 μ M) is about an order of
25 magnitude less than that of 5a. It should be noted that
the second series of cytotoxicity and tubulin
polymerization experiments were performed independently
of the first series in DMSO. Therefore, studies with
both 5a and combretastatin A-4 were repeated as internal
30 controls. In the cytotoxicity experiments significantly

1 higher ED₅₀ values were obtained for both compounds in
the later studies.

Next, major efforts were directed toward
replacement of the 4-OMe group of the B-ring. In this
line, seven cis stilbenes were prepared by substituting
5 the methoxy group with OEt, O-n-Pr, SMe, Me, Et, i-
propyl, or t-butyl groups (compounds 15a, 15b, 15c, 15d,
15e, 15f, and 15g, respectively). Substitution with a
large group like t-butyl or O-benzyl (15g and 15j)
10 resulted in the reduction of cytotoxicity by about 3 to
4 orders of magnitude and it greatly diminished ability
to inhibit tubulin polymerization (IC₅₀ > 40 μM).
However, the compounds 15a-f were highly cytotoxic in
all five cancer cell cultures, with potencies from 100
times less than to equal to that of combretastatin A-4.
15 Replacement of the OMe of the B-ring with an SMe group
(compound 15c) resulted in a compound which was as
cytotoxic as the parent compound 15a in the A-549 and
MLM cell cultures. However, the thiomethyl compound was
about one order of magnitude less cytotoxic than 5a in
20 the MCF cell culture, while being about one order of
magnitude more potent than 5a in HT-29 cells and two
orders of magnitude more potent in SKMEL-5 cells. The
thiomethyl compound 15c is an analogue of
25 thiocolchicine, which is more potent as a tubulin
polymerization inhibitor and is more cytotoxic in
certain cell cultures than colchicine. Substitution
with i-propyl (compound 15f) decreased the cytotoxicity
somewhat (ED₅₀ 7.0 x 10⁻² to 4.7 x 10⁻⁴ μM range), as did
substitution with an O-n-propyl group (compound 15b).
30 In addition to cytotoxicity, compounds 15a-f retained
significant tubulin polymerization inhibitory activity

1 relative to 5a. The decreased anti-tubulin activity of
the 4-isopropyl compound 15f and the lack of activity of
the 4-tert-butyl compound 15g demonstrates that an
increase in steric bulk at this position results in a
decrease in activity. Of particular interest is the
5 enhancement of antitubulin activity which occurred with
a reduction in size of the 4-substituent in the B-ring.
The only new compound more effective than the parent
compound 5a as an inhibitor of tubulin polymerization
was 15d, in which a methyl group replaced the 4-methoxy
10 group of 5a. The potency of this agent as a tubulin
polymerization inhibitor was equivalent to
combretastatin A-4 (1b), the natural product, even
though it lacks the adjacent hydroxyl group in the B-
ring.

15 Consistent with earlier observations, all the
trans stilbenes (compounds 16a-1) were less potent than
their corresponding cis isomers. Compounds 16a, 16c and
16f showed moderate cytotoxicity (in 1.0×10^{-1} μ M range)
in at least three cell lines and the other compounds
20 were less potent.

Turning to the cis stilbenes with substitution
on the olefinic bridge (Table V), introduction of
substitutions on either the 1 or 2 position of the
olefin reduced the cytotoxicity by from one to at least
25 5 orders of magnitude. In separate experiments, a COOH
group was introduced on position 1 or 2 of the olefinic
linkage and this resulted in the formation of compounds
23a and 23c (ED_{50} 1.9 to > 25 μ M). However, when the
COOH group of compound 23a was converted to the methyl
30 ester (compound 24a) or the N-methylamide (compound
24c), the cytotoxicity increased 2 to 3 orders of

1 magnitude in at least four cell cultures (as compared to
23a). Compounds 24a and 24c had ED_{50} values of 5.0×10^{-2} to $6.4 \times 10^{-3} \mu M$ in A-549, MCF-7, HT-29, and SKMEL-5
cell cultures. However, the dimethylaminoethyl or
diethylaminoethyl esters (compounds 24e and 24f) or the
5 N-ethylamide (compound 24d) of compound 23a did not show
considerable cytotoxicity. Transfer of the B-ring
methoxy group in compound 23a to the 3-position
(compound 23b) resulted in about 10 to 100-fold increase
in the cytotoxicity in three cell lines and similar
10 movement in compound 24a (compound 24b) reduced the
cytotoxicity by 100 to 1000-fold.

Among the dihydrostilbene analogues of 8a
(Table III), five compounds (17a, 17c-e and 17h) had ED_{50}
values of less than $1 \mu M$ in at least four cell lines,
15 with 3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-
propanonitrile (17h) being the most potent, both as a
cytotoxic agent and as a tubulin polymerization
inhibitor. However, this compound was about 10 to 100-
fold less cytotoxic than 1-(4-methoxyphenyl)-2-(3,4,5-
20 trimethoxyphenyl)ethane (8a), although its activity as a
tubulin polymerization inhibitor (IC_{50} $11 \mu M$) was not
decreased much relative to that of 8a (IC_{50} $7.9 \mu M$).
While in the cis stilbene series, substitution of the B-
ring methoxy with ethoxy, methyl, or ethyl reduced
25 cytotoxicity by a maximum of two orders of magnitude,
similar changes in the dihydrostilbene derivatives
(compounds 17a, 17d and 17e) reduced cytotoxicity about
100 to 1000-fold. These dihydro compounds were also
less potent as tubulin polymerization inhibitors. In
30 the absence of the 3-hydroxyl group in the B-ring of
combretastatin A-4 we have routinely observed a much

1 larger loss of anti-tubulin activity upon reduction of
the cis-stilbene to the dihydrostilbene than the
approximately 50% loss of activity that occurs when
combretastatin A-4 is reduced. Similarly, substitution
5 with O-n-propyl, SMe, O(CH₂)₂NMe₂ or O(CH₂)₂NEt₂ groups
(compounds 17b, 17c, 17f and 17g) also decreased
cytotoxicity. Introduction of a CN group adjacent to
the A-ring of 8a (compound 17h) reduced cytotoxicity by
10 to 100-fold, but a similar introduction of CN group
adjacent to the B-ring (compound 17i) reduced
cytotoxicity by 10,000-fold and, in contrast to 17h, the
tubulin polymerization inhibitory activity of 17i (IC₅₀ >
40 μM) was compromised relative to that of 8a. This
relationship is identical to that observed when hydroxyl
15 groups were introduced into corresponding positions in
dihydrocombretastatin A-4. Conversion of the cyano
group in compound 17i to a COOMe group resulted in the
formation of a compound 17j (ED₅₀ > 25 μM in all cell
cultures, IC₅₀ > 40 μM in the tubulin polymerization
inhibition assay).

20 Several stilbenes and dihydrostilbenes
containing acidic and basic groups were synthesized in
an effort to obtain substances that could be more
readily formulated. Included were 17f-g, 23a-c and 24e-
f. None of these compounds inhibited tubulin
25 polymerization significantly, and they were also in
general not particularly cytotoxic.

In another set of modifications, the two-
carbon bridge in 1-(4-methoxyphenyl)-2-(3,4,5-
trimethoxyphenyl)ethane (8a) was reduced to a one carbon
30 bridge (compounds 27, 28 and 29, Table VI). All of
these compounds were less potent than 8a. 3,4,4',5-

1 Tetra-methoxybenzophenone (27) was about 100 times less
cytotoxic than 8a, although its tubulin polymerization
inhibitory activity (IC_{50} 7.4 μ M) was essentially
identical to that of 8a (IC_{50} 7.9 μ M). Conversion of 27
5 to the alcohol 28 reduced cytotoxicity by another 100
times and also resulted in lower tubulin polymerization
inhibitory activity (IC_{50} > 40 μ M). Hydrogenolysis of
alcohol 28 to 4-methoxyphenyl-(3,4,5-trimethoxy-
phenyl)methane (29) increased the activity in the MCF-7,
HT-29, and SKMEL systems to that comparable with 27, and
10 increased the activity in the A-549 and MLM cell
cultures. These effects on cytotoxicities were
reflected in the tubulin polymerization inhibitory
activity of 29 (IC_{50} 15 μ M) relative to that of 28 (IC_{50}
> 40 μ M).

15 The antitubulin activities of the
conformationally restricted analogues of the stilbene 5a
and the dihydrostilbene 8a are included in Table VII.
The data indicate that the active conformation of the
stilbene 5a does not approach being planar, and involves
20 a conformation in which at least one of the phenyl rings
is twisted out of the plane of the other phenyl ring.
In this context, it should be pointed out that the
planar conformation of 5a is a high energy species due
to a nonbonded interaction between the protons of the
25 two aromatic rings that are ortho to the bridge.
Consequently, a totally planar conformation of 5a is not
expected to exist to any appreciable extent. The X-ray
structure of combretastatin A-1 reveals that the normals
to the least squares planes of the two phenyl rings are
30 inclined 66° to each other. This likely represents a
low energy conformation which may be involved in binding

1 at the receptor site. Consistent with this hypothesis
is the well documented and recognized fact that the
planes of the trimethoxy-benzene ring and the other
oxygen-substituted ring in podophyllotoxin, colchicine,
5 steganacin, and combretastatin A-4 exist in similar
dihedral relationships, so that these natural products
resemble each other structurally to some extent when
bound at the receptor site.

The results also imply that in the active
conformation of 8a the dihedral angle between the two
10 bridge bonds connected to the aromatic rings approaches
0°, so that the conformation would resemble the
structure of the cis alkene 5a. This might explain the
lower activity of the indane derivative 35, since in
this case the dihedral angle between the relevant bonds
15 would be closer to 120°. The lower inactivity of the
benzylisoquinolines shown in Scheme XVI is more
difficult to rationalize on conformational grounds
because the benzyl group is more conformationally
mobile. However, the tetrahydroprotoberberine system 48
20 is more conformationally restricted, with a dihedral
angle between the relevant bonds labeled "a" and "b" in
structure 48 of about 165°.

The low activity of the compounds in Table VII
as tubulin polymerization inhibitors was reflected in
25 their low cytotoxicities. None of these compounds had
ED₅₀ values of less than 1 µM in any of the cell
cultures.

Modifications can be made in the structure of
combretastatin A-4 (1b) and its tetramethoxy analogue
30 (5a) without substantially comprising cytotoxic and
antitubulin activity. The cis-stilbene and

1 benzylaniline configuration is most preferred, and all
bridge substituents that have been tried to date reduce
activity. The methoxy groups at positions 3, 4 and 5 in
the A ring is preferred and substitution at positions 4
5 in the B ring is also highly preferred.

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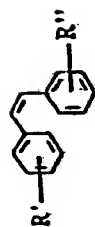
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Table I. Cis Stilbenes



No.	R'	R''	A-549	Cytotoxicity (ED ₅₀ in μ M) MCF-7	HT-29	SKMEL-5	MLM	mp °C
5a	3,4,5-(OMe) ₃	4-OMe	2.2 X 10 ⁻⁵	1.2 X 10 ⁻⁶	2.7 X 10 ⁻⁵	9.7 X 10 ⁻⁷	9.3 X 10 ⁻⁵	oil
5b	3,4,5-(OMe) ₃	3-OMe	1.3 X 10 ⁻¹	1.4 X 10 ⁻¹	9.0 X 10 ⁻²	6.0 X 10 ⁻²	1.4	oil
5c	3,4,5-(OMe) ₃	2-OMe	1.1	1.3	8.7 X 10 ⁻¹	1.2	8.6	oil
5d	2,3,4-(OMe) ₃	4-OMe	9.7 X 10 ⁻¹	2.3 X 10 ⁻¹	1.0	1.1	10.9	55-7
5e	3,4,5-(OMe) ₃	2-Cl-4-OMe	5.1 X 10 ⁻²	4.6 X 10 ⁻²	6.6 X 10 ⁻²	1.7 X 10 ⁻²	1.4 X 10 ⁻¹	oil
5f	3,4,5-(OMe) ₃	H	1.7 X 10 ⁻¹	2.5 X 10 ⁻¹	8.4 X 10 ⁻²	1.2 X 10 ⁻¹	>25	oil
5g	3,4,5-(OMe) ₃	4-Cl	8.0 X 10 ⁻²	1.8 X 10 ⁻¹	5.0 X 10 ⁻²	1.0 X 10 ⁻²	1.7 X 10 ⁻¹	oil
5h	3,4,5-(OMe) ₃	4-Br	1.1 X 10 ⁻²	1.6 X 10 ⁻²	8.2 X 10 ⁻³	6.7 X 10 ⁻³	1.4 X 10 ⁻²	oil
5i	1-(4-Pyridyl)-2-(3,4,5-trimethoxyphenyl)ethene		14.2	17.0	12.9	14.4	>25	oil
5j	1-(3-Pyridyl)-2-(3,4,5-trimethoxyphenyl)ethene		13.7	14.7	9.8	6.0	>25	oil
5k	1-(2-Pyridyl)-2-(3,4,5-trimethoxyphenyl)ethene		>25	>25	>25	>25	>25	oil
5l	3,4,5 (OMe) ₃	4-NO ₂	>25	>25	>25	>25	>25	140-2
5m	3,4,5-(OMe) ₃	4-OSi(<i>t</i> -Bu)Me ₂	10.95	7.29	10.60	7.59	17.23	oil
5n	3,4,5-(OMe) ₃	4-NMe ₂	4.1 X 10 ⁻³	5.8 X 10 ⁻³	8.1 X 10 ⁻³	1.5 X 10 ⁻⁴	9.4 X 10 ⁻³	oil
5o	3,4,5-(OMe) ₃	4-OH	12.70	5.70	1.75	2.27	12.60	148-150
5p	3,4,5-(OMe) ₃	4-OAc	1.7	3.0 X 10 ⁻¹	6.0	6.0 X 10 ⁻¹	6.3	oil
1a	Combretastatin A-4		1.2 X 10 ⁻⁶	3.8 X 10 ⁻⁶	1.2 X 10 ⁻⁵	3.0 X 10 ⁻⁸	1.4 X 10 ⁻⁵	-
	Adriamycin		2.9 X 10 ⁻²	3.1 X 10 ⁻²	5.5 X 10 ⁻²	3.2 X 10 ⁻²	1.3 X 10 ⁻¹	-

Table I continued

No.	R'	R''	Cytotoxicity (ED ₅₀ in μM)					MLM	mp °C
			A-549	MCF-7	HT-29	SKMEL-5			
15a	3,4,5-(OMe) ₃	4-OEt	1.6 x 10 ⁻³	9.6 x 10 ⁻²	1.8 x 10 ⁻³	2.5 x 10 ⁻³	2.9 x 10 ⁻²	oil	
15b	3,4,5-(OMe) ₃	4-OPr	3.9 x 10 ⁻²	6.6 x 10 ⁻¹	2.8 x 10 ⁻²	1.4 x 10 ⁻²	6.5 x 10 ⁻²	oil	
15c	3,4,5-(OMe) ₃	4-SMe	1.9 x 10 ⁻⁴	5.4 x 10 ⁻³	1.8 x 10 ⁻³	4.0 x 10 ⁻⁶	3.3 x 10 ⁻³	oil	
15d	3,4,5-(OMe) ₃	4-Me	9.4 x 10 ⁻⁴	2.4 x 10 ⁻²	2.3 x 10 ⁻³	8.5 x 10 ⁻⁴	6.6 x 10 ⁻³	oil	
15e	3,4,5-(OMe) ₃	4-Et	1.2 x 10 ⁻²	7.2 x 10 ⁻²	2.7 x 10 ⁻³	8.6 x 10 ⁻⁴	7.5 x 10 ⁻³	oil	
15f	3,4,5-(OMe) ₃	4-Pr	6.6 x 10 ⁻³	1.4 x 10 ⁻³	2.4 x 10 ⁻³	4.7 x 10 ⁻⁴	7.0 x 10 ⁻²	oil	
15g	3,4,5-(OMe) ₃	4-Bu	1.02	1.57	8.8 X 10 ⁻¹	2.1 X 10 ⁻¹	4.32	oil	
15h	3,4,5-(OMe) ₃	4-OMe	>25	>25	>25	>25	>25	oil	
15i	3,5-(OMe) ₂	4-OMe	1.3 x 10 ⁻¹	1.6 x 10 ⁻¹	3.4 x 10 ⁻¹	4.2 x 10 ⁻¹	9.8 x 10 ⁻²	oil	
16j	3,5-(OMe) ₂ ; 4-OBn	4-OMe	1.04	1.92	9.5 X 10 ⁻¹	6.1 X 10 ⁻¹	>25	oil	
15k	3,5-(OMe) ₂	4-OMe	>25	>25	9.0	>25	>25	oil	
15l	4-OSi(<i>i</i> -Bu)Me ₂	4-OMe	21.5	>25	8.7	0.6	>25	oil	
151	3,5-(OMe) ₂ ; 4-OAc	4-OMe							

Table II. Trans Stilbenes



6

No.	R'	R''	Cytotoxicity (ED ₅₀ in μ M)			MLM	mp °C
			MCF-7	HT-29	SKMEL-5		
6a	3,4,5-(OMe) ₃	4-OMe	1.05	1.82	8.1×10^{-1}	2.07	152-53 ³⁹
6b	3,4,5-(OMe) ₃	3-OMe	12.2	7.3	10.5	>25	123-5
6c	3,4,5-(OMe) ₃	2-OMe	18.0	12.1	13.5	>25	oil
6e	3,4,5-(OMe) ₃	2-Cl-4-OMe	>25	>25	>25	>25	oil
6f	3,4,5-(OMe) ₃	H	>25	>25	>25	>25	105-6 ²⁴
6g	3,4,5-(OMe) ₃	4-Cl	>25	>25	>25	>25	147-9
6h	3,4,5-(OMe) ₃	4-Br	9.14	12.69	6.53	5.13	155-6
6i	1-(4-Pyridyl)-2-(3,4,5-trimethoxyphenyl)ethene		>25	>25	>25	>25	247-8 ⁴⁷
6j	1-(3-Pyridyl)-2-(3,4,5-trimethoxyphenyl)ethene		>25	>25	>25	>25	105-5 ⁴⁸
6l	3,4,5-(OMe) ₃	4-NO ₂	>25	>25	>25	>25	192-4 ⁴⁰
6m	3,4,5-(OMe) ₃	4-OSi(<i>i</i> -Bu) ₂ Me ₂	>25	>25	>25	>25	oil
6n	3,4,5-(OMe) ₃	4-NMe ₂	6.1×10^{-3}	8.2×10^{-2}	4.6×10^{-3}	1.25×10^{-2}	114-5
6o	3,4,5-(OMe) ₃	4-OH	18.63	>25	11.55	24.15	188-90 ⁴
6p	3,4,5-(OMe) ₃	4-OAc	9.6	5.4	4.6	13.0	oil
6q	3,4-(OMe) ₂	H	>25	>25	>25	>25	106-8 ⁴¹
6r	2,3,4-(OMe) ₃	H	>25	>25	>25	>25	79-82
6s	3,4,5-(OMe) ₃	3,5-(OMe) ₂	>25	>25	>25	>25	132-4 ⁴⁹

Table II. Trans Stilbenes (cont.)



6

No.	R'	R''	Cytotoxicity (ED ₅₀ in μ M)				MLM	mp °C
			A-549	MCF-7	HT-29	SK-MEL-5		
6t	3,4,5-(OMe) ₃	2,3,4-(OMe) ₃	12.5	14.72	10.27	10.64	23.86	87-8
6u	3,4,5-(OMe) ₃	3,4,5-(OMe) ₃	>25	>25	>25	>25	>25	174-5 ⁵⁰
6v	3,4,5-(OMe) ₃	2,4,5-(OMe) ₃	>25	>25	>25	>25	>25	147-8
6w	2,4,5-(OMe) ₃	H	>25	8.5	>25	>25	>25	81-2
6x	2,4,6-(OMe) ₃	H	>25	>25	>25	>25	>25	57-9 ^{51,52}
6y	3,4-(OMe) ₂	3,5-(OMe) ₂	>25	>25	>25	>25	>25	65-7 ⁴⁹
6z	3,4,5-(OMe) ₃	NH ₂	>25	>25	>25	>25	>25	251-3
Adriamycin			2.9 X 10 ⁻²	3.1 X 10 ⁻²	5.5 X 10 ⁻²	3.2 X 10 ⁻²	1.3 X 10 ⁻¹	-

Table II continued

No.	R'	R''	Cytotoxicity (ED ₅₀ in μ M)					mp °C
			A-549	MCF-7	HT-29	SKMEL-5	MLM	
16a	3,4,5-(OMe) ₃	4-OEt	1.7 X 10 ⁻¹	7.5 X 10 ⁻¹	1.49	1.17	2.2 X 10 ⁻¹	87-88
16b	3,4,5-(OMe) ₃	4-OPr	9.2	12.5	>25	>25	>25	82-83
16c	3,4,5-(OMe) ₃	4-SMe	4.7 X 10 ⁻¹	5.9 X 10 ⁻²	8.3 X 10 ⁻²	2.8 X 10 ⁻¹	7.3	109-111
16d	3,4,5-(OMe) ₃	4-Me	1.1	1.9	9.0 X 10 ⁻¹	8.0 X 10 ⁻¹	6.3	125-127
16e	3,4,5-(OMe) ₃	4-Et	1.3 X 10 ⁻¹	1.2	1.1 X 10 ⁻¹	1.7 X 10 ⁻¹	2.2 X 10 ⁻¹	97-99
16f	3,4,5-(OMe) ₃	4-Pr	5.8	18.4	6.8	11.1	>25	74-75
16g	3,4,5-(OMe) ₃	4-Bu	>25	>25	>25	>25	>25	127-128
16h	3,4-(OMe) ₂	4-OMe	11.7	>25	>25	>25	>25	135-137
16i	3,5-(OMe) ₂	4-OMe	7.5	9.7	6.9	8.8 X 10 ⁻¹	>25	55-56
16j	3,5-(OMe) ₂ 4-OBn	4-OMe	>25	>25	17.8	>25	>25	104-105
16k	2,3-(OMe) ₂ 4-OSi(<i>i</i> -Bu)Me ₂	4-OMe	>25	>25	>25	>25	>25	118-120
16l	3,5-(OMe) ₂ ; 4-OAc	4-OMe	16.4	19.4	11.7	10.2	21	129-131

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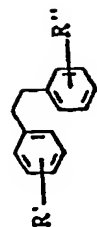
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Table III. Dihydrostilbenes



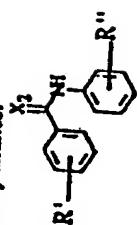
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No.	R'	R''	A-549	Cytotoxicity (ED ₅₀ in μ M) MCF-7	HT-29	SKMEL-5	MLM	mp °C
8a	3,4,5-(OMe) ₃	4-OMe	1.8×10^{-4}	1.6×10^{-4}	2.5×10^{-4}	1.4×10^{-4}	1.8×10^{-4}	73-53 ³⁹
8b	3,4,5-(OMe) ₃	3-OMe	11.7	12.4	7.6	9.2	>25	oil
8c	3,4,5-(OMe) ₃	2-OMe	13.5	11.8	>25	20	>25	oil
8d	3,4,5-(OMe) ₃	H	>25	>25	>25	>25	>25	oil
8e	3,4,5-(OMe) ₃	H	>25	>25	>25	>25	>25	oil ⁴⁵
8f	1-(4-Pyridyl)-2-(3,4,5-trimethoxyphenyl)ethane		12.2	>25	>25	>25	>25	112-4
8g	1-(3-Pyridyl)-2-(3,4,5-trimethoxyphenyl)ethane		>25	>25	>25	>25	>25	oil
8h	3,4,5-(OMe) ₃	4-NHCOCH ₃	8.3×10^{-2}	6.4×10^{-2}	7.7×10^{-2}	5.9×10^{-2}	1.2×10^{-1}	108-110 ⁶
8i	3,4,5-(OMe) ₃	4-NMe ₂	>25	>25	>25	>25	>25	oil
8j	3,4,5-(OMe) ₃	4-OH	19.0	>25	>25	>25	>25	oil
8k	3,4,5-(OMe) ₃	4-OAc	>25	>25	>25	>25	>25	oil
8l	3,4-(OMe) ₂	H	>25	>25	>25	>25	>25	76-74 ⁹
8m	2,3,4-(OMe) ₃	H	>25	>25	>25	>25	>25	oil
8n	3,4,5-(OMe) ₃	3,5-(OMe) ₂	>25	>25	>25	>25	>25	137-83 ³³
8o	3,4,5-(OMe) ₃	2,3,4-(OMe) ₃	>25	>25	>25	>25	>25	88-9
8p	3,4,5-(OMe) ₃	3,4,5-(OMe) ₃	>25	>25	>25	>25	>25	84-5
8q	3,4,5-(OMe) ₃	2,4,5-(OMe) ₃	>25	>25	>25	>25	>25	-
8r	3,4,5-(OMe) ₃	4-NH ₂	12.23	11.88	24.56	12.65	>25	-
8s	3,4,5-(OMe) ₃	4-NH ₂	1.0×10^{-2}	3.3×10^{-1}	8.1×10^{-3}	2.1×10^{-3}	1.0×10^{-2}	-
8t	3,4,5-(OMe) ₃	Dihydrocembresterin A-4	2.9×10^{-2}	3.1×10^{-2}	5.5×10^{-2}	3.2×10^{-2}	1.3×10^{-1}	-
8u	3,4,5-(OMe) ₃	Adriamycin						

Table III continued

No.	R'	Y	Z	Cytotoxicity (ED ₅₀ in μ M) R"	A-549	MCF-7	HT-29	SK-MEL-5	MLM	mp °C
17a	3,4,5-(OMe) ₃	H	H	4-OEt	1.9 X 10 ⁻¹	1.9 X 10 ⁻¹	1.8 X 10 ⁻¹	1.7 X 10 ⁻¹	2.7 X 10 ⁻¹	oil
17b	3,4,5-(OMe) ₃	H	H	4-OPr ⁿ	7.2	3.9	6.4	6.7	15.0	oil
17c	3,4,5-(OMe) ₃	H	H	4-SMe	1.5 X 10 ⁻¹	2.0 X 10 ⁻¹	4.0 X 10 ⁻¹	2.4 X 10 ⁻¹	1.3	52-54
17d	3,4,5-(OMe) ₃	H	H	4-Me	1.8 X 10 ⁻¹	2.2 X 10 ⁻¹	1.0 X 10 ⁻¹	2.7 X 10 ⁻¹	1.4	51-52
17e	3,4,5-(OMe) ₃	H	H	4-Et	8.8 X 10 ⁻²	1.6 X 10 ⁻¹	1.6 X 10 ⁻²	4.7 X 10 ⁻²	2.7 X 10 ⁻¹	oil
17f	3,4,5-(OMe) ₃	H	H	4-O(CH ₂) ₂ NMe ₂	>25	10.3	9.8	11.4	>25	oil
17g	3,4,5-(OMe) ₃	H	H	4-O(CH ₂) ₂ NEt ₂	6.8	4.3	5.2	8.5	>25	oil
17h	3,4,5-(OMe) ₃	CN	H	4-OMe	9.6 X 10 ⁻³	1.4 X 10 ⁻²	7.5 X 10 ⁻³	4.1 X 10 ⁻³	1.6 X 10 ⁻²	82-83
17i	3,4,5-(OMe) ₃	H	CN	4-OMe	11.5	14.3	9.4	6.4	21.1	102-103
17j	3,4,5-(OMe) ₃	H	COOMe	4-OMe	>25	>25	>25	>25	>25	84-85

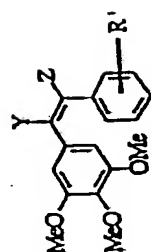
Table IV. Benzamides and Benzylamines.



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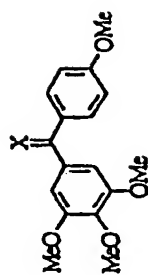
No.	R'	R''	X ₂	A-549	Cytotoxicity (ED ₅₀ in μM) MCF-7	HT-29	SKMEL-5	MLM	mp °C
11a	3,4,5-(OMe) ₃	4-OMe	O	14.07	12.21	22.65	>25	>25	160-142
11b	3,4-(OMe) ₂	3,4,5-(OMe) ₃	O	>25	>25	>25	>25	>25	155-6
11c	4-OMe	3,4,5-(OMe) ₃	O	>25	>25	>25	>25	>25	159-160
11d	3,5-(OMe) ₂	4-OMe	O	9.02	5.47	14.52	11.88	>25	104-5
11e	4-OMe	3,5-(OMe) ₂	O	>25	>25	>25	>25	>25	105-6
11f	3,4,5-(OMe) ₃	3,4,5-(OMe) ₃	O	>25	>25	>25	>25	>25	211-2
12a	3,4,5-(OMe) ₃	4-OMe	H ₂	1.9 X 10 ⁻³	2.4 X 10 ⁻³	1.0 X 10 ⁻³	7.0 X 10 ⁻⁴	1.6 X 10 ⁻³	73-4
12b	3,4-(OMe) ₂	3,4,5-(OMe) ₃	H ₂	>25	>25	>25	>25	>25	oil
12c	4-OMe	3,4,5-(OMe) ₃	H ₂	8.3 X 10 ⁻¹	8.6 X 10 ⁻¹	2.24	1.13	>25	77-8
12d	3,5-(OMe) ₂	4-OMe	H ₂	5.71	6.08	17.84	2.41	>25	oil
12e	4-OMe	3,5-(OMe) ₂	H ₂	>25	>25	>25	>25	>25	oil
12f	3,4,5-(OMe) ₃	3,4,5-(OMe) ₃	H ₂	>25	>25	>25	>25	>25	127-8
Adriamycin				2.9 X 10 ⁻²	3.1 X 10 ⁻²	5.5 X 10 ⁻²	3.2 X 10 ⁻²	1.3 X 10 ⁻¹	-

Table V



No.	Y	Z	R'	Cytotoxicity (ED ₅₀ in μ M)				MLM	mp °C	Inhibition of Tubulin Polymerization IC ₅₀ (μ M) (\pm S.D.)
				A-549	MCF-7	HT-29	SK-MEL-5			
23a	COOH	H	4-OMe	15.9	12.8	8.4	9.1	>25	187-189	>40
23b	COOH	H	3-OMe	2.5 X 10 ⁻²	>25	1.2 X 10 ⁻¹	5.0 X 10 ⁻³	>25	176-180	>40
23c	H	COOH	4-OMe	5.2	1.9	5.9	2.3	>25	206-207	>40
24a	COOMe	H	4-OMe	1.1 X 10 ⁻²	2.0 X 10 ⁻²	9.5 X 10 ⁻³	6.4 X 10 ⁻³	9.6	74-75	>40
24b	COOMe	H	3-OMe	1.3	1.3	7.0 X 10 ⁻¹	1.5	15.5	87-88	>40
24c	CONHMe	H	4-OMe	2.4 X 10 ⁻²	5.0 X 10 ⁻²	2.6 X 10 ⁻²	2.4 X 10 ⁻²	9.3	172-174	35 (\pm 2)
24d	CONHEt	H	4-OMe	3.4	3.7	1.8	7.05	>25	152-154	>40
24e	COO(CH ₂) ₂ NEt ₂	H	4-OMe	1.8	2.1	2.8	2.7	>25	oil	>40
24f	COO(CH ₂) ₂ NMe ₂	H	4-OMe	7.7	10.4	>25	6.7	>25	oil	>40
	H	H	4-OMe	3.7 X 10 ⁻¹	6.2 X 10 ⁻⁴	2.6 X 10 ⁻⁴	2.6 X 10 ⁻⁴	1.6 X 10 ⁻³	oil	2.5 (\pm 0.8)

TABLE VI



No.	X	Cytotoxicity (ED ₅₀ in μ M)				mp °C	Inhibition of Tubulin Polymerization IC ₅₀ (μ M) (\pm S.D.)
		A-549	MCF-7	HT-29	SKMEL-5	MLM	
27	O	1.1 X 10 ⁻²	1.5 X 10 ⁻²	1.3 X 10 ⁻²	1.2 X 10 ⁻²	1.3 X 10 ⁻²	7.4 (\pm 0.4)
28	H, OH	1.5	1.9	1.2	1.5	16.8	>40
29	H ₂	1.5 X 10 ⁻¹	1.9 X 10 ⁻²	1.3 X 10 ⁻²	1.2 X 10 ⁻²	1.3 X 10 ⁻¹	15 (\pm 0.5)

Table VII

No.	Cytotoxicity (ED ₅₀ in μ M)				mp °C	Inhibition of Tubulin Polymerization IC ₅₀ (μ M) (\pm S. D.)
	A-549	MCF-7	HT-29	SKMEL-5	MLM	
32a	5.7	1.8	1.9	1.3	21.4	>40
32b	>25	>25	1.1	12.5	>25	>40
32c	>25	>25	>25	>25	>25	>40
32d	>25	14.6	9.3	12.0	>25	>40
33	14.3	>25	9.4	7.4	>25	>40
34	>25	>25	>25	>25	>25	>40
35	>25	>25	12.8	19.5	>25	>40
37	19.5	>25	20.5	2.1	180-2	>40
38	>25	>25	20.2	>25	>25	>40
39	>25	>25	>25	>25	>25	>40
40	>25	>25	9.7	8.8	>25	>40
41	11.4	22.7	>25	>25	196-8	>40
42	>25	>25	>25	>25	104-6	>40
48	>25	>25	>25	>25	>25	>40

Table VIII

Effects of compounds 5a, 5b, 5e, 5f, 5g, 5h, 5n, 5p, 6a, 6n, 8a, 8n, 12a, 12c and 12d on tubulin polymerization and on the binding of radiolabeled colchicine to tubulin

compd	Tubulin polymerization IC ₅₀ (μM) (± S. D.)	Colchicine binding % inhibition
5a	2.2 (± 0.07)	95
5b	8.8 (± 1)	50
5e	3.5 (± 0.3)	73
5f	36 (± 1)	14
5g	4.8 (± 0.3)	55
5h	3.1 (± 0.1)	73
5n	3.4 (± 0.1)	83
5p	29 (± 5)	24
6a	>50	—
6n	>50	—
8a	7.9 (± 0.8)	65
8n	29 (± 1)	31
12a	23 (± 0.5)	34
12c	>50	—
12d	29 (± 7)	39
Combretastatin A-4 (1a)	1.9 (± 0.2)	99
1b	>50	—
1c	3.3 (± 0.2)	79
Podophyllotoxin	2.1 (± 0.1)	88
Thiocolchicine	1.4 (± 0.08)	57

The IC₅₀ values for tubulin polymerization was determined as described in the text, with full details presented elsewhere.³¹ For the colchicine binding assay, reaction mixtures (in triplicate) contained 1 μM tubulin, 5 μM [³H]colchicine, and 5 μM inhibitor and were incubated for 10 min at 37 °C prior to analysis. Further details have been described previously.³²

1 Table IX

5	Compound No.	Inhibition of Tubulin Polymerization IC ₅₀ (μ M)(\pm SD)
<hr/>		
	5a ^a	2.5 (\pm 0.1)
	Combretastatin A-4 ^a	2.0 (\pm 0.3)
	15a	2.7 (\pm 0.2)
10	15b	6.0 (\pm 0.8)
	15c	6.2 (\pm 0.5)
	15d	2.0 (\pm 0.2)
	15e	3.4 (\pm 0.3)
	15f	12 (\pm 2)
	15g	> 40
	15h	18 (\pm 0.6)
	15i	3.8 (\pm 0.3)
15	15j	> 40
	15k	> 40
	15l	24 (\pm 5)
	16a-16l	> 40
	17a	10 (\pm 1)
	17b	> 40
	17c	> 40
20	17d	21 (\pm 3)
	17e	18 (\pm 1)
	17f	> 40
	17g	> 40
	17h	11 (\pm 0.4)
	17i	> 40
	17j	> 40
	23a-23c	> 40
25	24a, b, d-f	> 40
	24c	35 (\pm 2)
	27	7.4 (\pm 0.4)
	28	> 40
	29	15 (\pm 0.5)
	32a-32d	> 40
	33-35, 37-42, 48	> 40

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* A second set of experiments was performed with these compounds for the studies presented in this Table.

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Table X. Cytotoxicities and Antitubulin Activities of Schiff Bases, Benzanilines, and Benzaniline Hydrochlorides

no.	cytotoxicity (GI ₅₀ in μM) ^a							inhibition of tubulin polymerization (GI ₅₀) ^b
	HL-60 (TB)	NCI-H522	DMS 273	COLO 205	SF-295	M14	OVCAR-3	
108b	21.6	>100	>100	49.1	>100	>100	>100	>40
108c	26.8	>100	33.0	28.6	52.7	83.8	>100	>40
108d	>100	>100	>100	75.9	>100	>100	>100	>40
108f	>100	>100	52.5	>100	>100	>100	>100	>40
108g	22.6	>100	>100	>100	>100	>100	>100	6.0 (± 0.6)
109a	0.122	0.195	0.0926	0.152	0.163	0.150	0.184	0.192
109b	0.168	0.234	0.135	0.344	0.266	0.315	0.283	0.354
109c	0.115	0.412	0.141	0.235	0.266	0.403	0.363	0.458
109d	0.296	0.380	0.296	0.432	0.274	5.26	5.93	2.04
109e	3.70	4.68	3.09	3.88	7.28	0.292	0.214	32.0
109f	0.0722	0.262	0.104	0.219	0.233	0.437	0.405	>40
110a	0.245	0.371	0.318	0.352	0.339	2.38	1.96	3.5 (± 0.05)
110b	0.834	2.76	0.534	1.66	2.32	0.532	0.464	7.2 (± 0.4)
110c	0.448	0.574	0.961	0.538	0.418	4.84	4.85	8.9 (± 0.5)
110d	3.29	2.95	4.91	3.60	3.41	16.9	16.3	11 (± 0.6)
110e	14.4	11.1	12.9	17.9	20.9	22.4	16.3	16 (± 2)
110f	14.1	17.3	16.2	19.0	10.5	19.0	19.0	>40
110g								>40

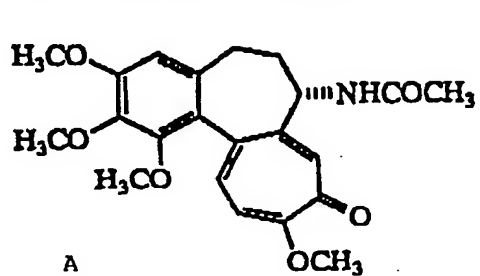
^aGI₅₀ values are the averages of two determinations.

^aThe cytotoxicity GI₅₀ values are the concentrations corresponding to 50% growth inhibition, and they are the averages of two determinations.

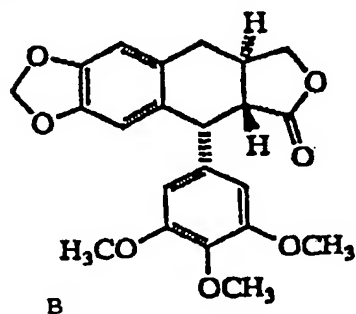
^bThe tubulin polymerization assay used in the studies presented here employs 1 M microtubule glutamate and GTP to induce the assembly of tubulin polymerization. Although the reaction conditions are identical in the current studies to those described earlier a different glutamate preparation was used. This modification has caused a reduction in all IC₅₀ values obtained with antimitotic compounds. The reason for the change is presently not known. Several standard agents were evaluated for comparison with the new compounds described here. The following IC₅₀ values were obtained: colchicine (A), 1.90-2.2 μ M; podophyllotoxin (B), 1.30-0.06 μ M; taxastatin A-4 (D), 1.00-0.06 μ M; and compound E, 1.20-0.05 μ M.

In the footnote of footer b, A, B, D and E are as follows:

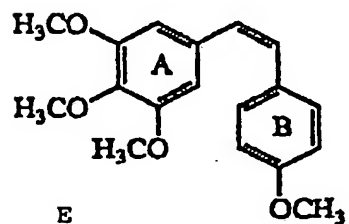
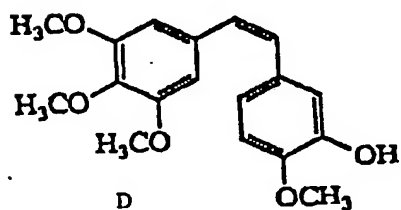
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Table XI. Cytotoxicities of 4-Methyl-N-(3,4,5-trimethoxybenzyl)aniline hydrochloride (110a)

Panel/Cell Line	Log10 OI50
Leukemia	
CCRF-CBM	-6.55
HL-60 (TB)	-7.05
K-562	-7.00
MOLT-4	-6.37
RPMI-8226	-6.36
Non-Small Cell Lung Cancer	
A549/ATCC	-6.29
HKC8	-6.13
HOP-18	-4.43
HOP-62	-6.55
HOP-92	-4.73
NCI-H23	-6.39
NCI-H322M	-6.30
NCI-H460	-6.67
NCI-H522	-6.69
LXFL 329	-6.20
Small Cell Lung Cancer	
DMS114	-6.37
DMS 273	-7.03
Colon Cancer	
COLO 205	-6.67
DLD-1	-6.24
HCT-116	-6.24
HCT-15	-6.61
HT29	-6.46
KM12	-6.12
KM20L2	-6.60
SW-620	-6.96
CNS Cancer	
SF-268	-6.04
SF-295	-6.49
SF-539	-6.50
SNB-19	-6.53
SNB-75	-6.41
SNB-78	-5.96
U251	-6.48
XP 498	-6.33
Melanoma	
LOX IMVI	-6.07
MALME-3M	-6.33
M14	< -8.00
M19-MEL	-6.48
SK-MEL-2	-6.88
SK-MEL-3	-6.04
UACC-257	> -4.00
UACC-62	-6.24
Ovarian Cancer	
IGROV1	-6.15
OVCAR-3	-6.71
OVCAR-4	-4.67
OVCAR-5	-5.87
OVCAR-8	-6.12
SK-OV-3	-6.57
Renal Cancer	
786-O	-6.49
A498	> -4.00
ACHN	-7.01
CAKI-1	-7.88
RXP-393	-6.95
SN12C	-6.07
TK-10	> -4.00
UO-31	-6.08

Other benzyranilines have also been tested.
1 The results are indicated in Table X. More
specifically, the effects on cell growth and tubulin
polymerization of five Schiff bases 108, five amines
5 109, and seven hydrochlorides 110 are summarized in
Table X. These compounds were examined for cytotoxicity
in the human cancer cell lines HL-60 (TB) leukemia, NCI-
H522 non-small cell lung cancer, DMS 273 small cell lung
cancer, COLO 205 colon cancer, SF-295 CNS cancer, M14
10 melanoma, OVCAR-3 ovarian cancer, and CAKI-1 renal
cancer using the assays described hereinabove.
Inhibitor of tubulin polymerization was examined using
electrophoretically homogeneous tubulin from bovine
brain, using the assays described hereinabove.

With the amines 109a-e and the corresponding
15 hydrochloride salts 110a-g, potency as a tubulin
polymerization inhibitor inversely correlated with the
size of the R substituent in the C-4 position of the
aniline ring. The smaller the substituent, the higher
the potency. Among the highly soluble hydrochloride
20 salts, 4-methyl-N-(3,4,5-trimethoxybenzyl)aniline
hydrochloride (110a) was the most potent of the
compounds studied (IC_{50} 3.5 μ m). The 4-ethyl (110b, IC_{50}
7.2 μ m), 4-methoxy (110c, 8.9 μ m), 4-ethoxy (110d,
11.0 μ m), and 4-thiomethyl (110e, 16.0 μ m) analogues had
25 less activity. This trend between the potencies of the
compounds as tubulin polymerization inhibitors and the
size of the aniline substituent R was reflected
remarkably well by the cytotoxicities in all of the
cancer cell cultures studied. The smaller the
30 substituent, the higher the cytotoxicity. These
relationships generally held for the corresponding free

1 bases 109a-e, except that the compound with the ethyl
substituent (109b) was more effective (IC_{50} 3.0 μ m)
against tubulin polymerization than the analog with the
methyl substituent (109a, IC_{50} 6.0 μ m).

5 A more extensive analysis of the
cytotoxicities of the most potent benzylaniline
hydrochloride 110a is detailed in Table XI. A total of
55 cell lines from the leukemia, non-small cell lung
cancer, small cell lung cancer, colon cancer, CNS
10 cancer, melanoma, ovarian cancer, and renal cancer
panels were examined. As can be seen from the results
in Table XI, the cytotoxicity was broad in scope,
although 110a was clearly most cytotoxic ($\log_{10} GI_{50}$
< -7.00) in the HL-60 (TB) leukemia, K-562 leukemia, DMS
15 273 small cell lung cancer, M14 melanoma, ACHN renal
cancer, and CAKI-1 renal cancer cell cultures. It
therefore appears that benzylaniline hydrochloride salt
110a is an uncommonly simple, water soluble tubulin
polymerization inhibitor which is cytotoxic to a variety
20 of animal cancer models.

Without wishing to be bound to any mechanism,
the compounds encompassed in Formula I have been
determined to be effective inhibitors of tubulin
polymerization. In other words, the compounds of the
present invention interact effectively with the
25 colchicine binding site of tubulin thus they represent
potential antimitotic agents which may inhibit cancer
cell proliferation.

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1 Pharmaceutical Formulations

2 The present new compounds form salts with
3 acids when a basic amino function is present and salts
4 with bases when an acid function, i.e., carboxyl, is
5 present. All such salts are useful in the isolation
6 and/or purification of the new products. Of particular
7 value are the pharmaceutically acceptable salts with
8 both acids and bases. Suitable acids include, for
9 example, hydrochloric, sulfuric, nitric,
10 benzenesulfonic, toluene-sulfonic, acetic, maleic,
11 tartaric and the like which are pharmaceutically
12 acceptable. Basic salts for pharmaceutical use are the
13 Na, K, Ca and Mg salts, and the like.

14 The pharmaceutical compositions of the present
15 invention comprise the compounds encompassed by Formula
16 I and an acceptable pharmaceutical carrier. The carrier
17 can be any of those conventionally used and is limited
18 only by chemico-physical considerations such as
19 solubility and lack of reactivity with the compound and
20 by the route of administration.

21 For intravenous administration, the carrier
22 will be aqueous and may contain solubilizing agents,
23 buffers, preservatives, antioxidants, chelating agents,
24 and agents to control the tonicity, such as dextrose or
25 sodium chloride. The requirements for effective
26 pharmaceutical carriers for injectable compositions are
27 well known to one of ordinary skill in this art. (See
28 "Pharmaceutics and Pharmacy Practice", J.B. Lippincott
29 Company, Philadelphia, 1982, edited by Banker and
30 Chalmers, pages 238-250, which are incorporated by
31 reference, also see ASHP "Handbook of Injectable Drugs"
32 4th Edition by Trissel, pages 622-630, which lists

1 commercially available intravenous infusion solutions,
these pages are incorporated by reference.)

5 The active ingredients of the therapeutic
compositions and the compounds of the present invention
exhibit excellent anti-cancer activity when administered
in amounts ranging from about 0.001 mg to about 10.0 mg
per kilogram of body weight per day. A preferred dosage
10 regimen for optimum results would be from about 0.01 mg
to about 10 mg per kilogram of body weight per day, and
such dosage units are employed that a total of from
about 0.1 mg to about 1.0 mg per kilogram of the active
compound for a subject of about 70 kg of body weight are
15 administered in a 24-hour period in single or divided
doses. This dosage regimen may be adjusted to provide
the optimum therapeutic response and is preferably
administered one to three times a day. For example,
several divided doses may be administered daily or the
dose may be proportionally reduced as indicated by the
exigencies of the therapeutic situation. A decided
20 practical advantage is that the active compound may be
administered in a convenient manner such as by the oral,
intravenous (where water soluble), intramuscular or
subcutaneous routes.

The active compound may be orally
25 administered, for example, with an inert diluent or with
an assimilable edible carrier, or it may be enclosed in
hard or soft shell gelatin capsule, or it may be
compressed into tablets, or it may be incorporated
directly with the food of the diet. For oral
30 therapeutic administration, the active compound may be
incorporated with excipients and used in the form of
ingestible tablets, buccal tablets, troches, capsules,

1 elixirs, suspensions, syrups, wafers, and the like.
Such compositions and preparations should contain at
least 1 % of active compound. The percentage of the
compositions and preparations may, of course, be varied
5 and may conveniently be between about 5 to about 80 % of
the weight of the unit. The amount of active compound
in such therapeutically useful compositions is such that
a suitable dosage will be obtained. Preferred
compositions or preparations according to the present
10 invention are prepared so that an oral dosage unit form
contains between 5 and 1000 mg of active compound.

The tablets, troches, pills, capsules and the
like may also contain the following: A binder such as
gum tragacanth, acacia, corn starch or gelatin;
15 excipients such as dicalcium phosphate; a disintegrating
agent such as corn starch, potato starch, alginic acid
and the like; a lubricant such as magnesium stearate;
and a sweetening agent such as sucrose, lactose or
saccharin may be added or a flavoring agent such as
20 peppermint, oil of wintergreen, or cherry flavoring.
When the dosage unit form is a capsule, it may contain,
in addition to materials of the above type, a liquid
carrier. Various other materials may be present as
coatings or to otherwise modify the physical form of the
dosage unit. For instance, tablets, pills, or capsules
25 may be coated with shellac, sugar or both. A syrup or
elixir may contain the active compound, sucrose as a
sweetening agent, methyl and propylparabens as
preservatives, a dye and flavoring such as cherry or
orange flavor. Of course, any material used in
30 preparing any dosage unit form should be
pharmaceutically pure and substantially non-toxic in the

1 amounts employed. In addition, the active compound may
be incorporated into sustained-release preparations and
formulations. For example, sustained release dosage
5 forms are contemplated wherein the active ingredient is
bound to an ion exchange resin which, optionally, can be
coated with a diffusion barrier coating to modify the
release properties of the resin.

The active compound may also be administered
parenterally or intraperitoneally. Dispersions can also
10 be prepared in glycerol, liquid polyethylene glycols,
and mixtures thereof and in oils. Under ordinary
conditions of storage and use, these preparations
contain a preservative to prevent the growth of
microorganisms.

The pharmaceutical forms suitable for
15 injectable use include sterile aqueous solutions (where
water soluble) or dispersions and sterile powders for
the extemporaneous preparation of sterile injectable
solutions or dispersions. In all cases the form must be
sterile and must be fluid to the extent that easy
20 syringability exists. It must be stable under the
conditions of manufacture and storage and must be
preserved against the contaminating action of
microorganisms such as bacteria and fungi. The carrier
can be a solvent or dispersion medium containing, for
25 example, water, ethanol, polyol (for example, glycerol,
propylene glycol, and liquid polyethylene glycol, and
the like), suitable mixtures thereof, and vegetable
oils. The proper fluidity can be maintained, for
example, but the use of a coating such as lecithin; by
30 the maintenance of the required particle size in the
case of dispersion and by the use of surfactants. The

1 prevention of the action of microorganisms can be
brought about by various antibacterial and antifungal
agents, for example, parabens, chlorobutanol, phenol,
sorbic acid, thimerosal, and the like. In many cases,
5 it will be preferable to include isotonic agents, for
example, sugars or sodium chloride. Prolonged
absorption of the injectable compositions can be brought
about by the use in the compositions of agents delaying
absorption, for example, aluminum monostearate and
10 gelatin.

Sterile injectable solutions are prepared by
incorporating the active compound in the required amount
in the appropriate solvent with various of the other
ingredients enumerated above, as required, followed by
15 filtered sterilization. Generally, dispersions are
prepared by incorporating the various sterilized active
ingredient into a sterile vehicle which contains the
basic dispersion medium and the required other
ingredients from those enumerated above. In the case of
20 sterile powders for the preparation of sterile
injectable solutions, the preferred methods of
preparation are vacuum drying and the freeze-drying
technique which yield a powder of the active ingredient
plus any additional desired ingredient from previously
sterile-filtered solution thereof.

25 As used herein, "pharmaceutically acceptable
carrier" includes any and all solvents, dispersion
media, coatings, antibacterial and antifungal agents,
isotonic and absorption delaying agents, and the like.
The use of such media and agents for pharmaceutical
30 active substances is well known in the art. Except
insofar as any conventional media or agent is

1 incompatible with the active ingredient, its use in the
therapeutic compositions is contemplated. Supplementary
active ingredients can also be incorporated into the
compositions.

5 It is especially advantageous to formulate
parenteral compositions in dosage unit form for ease of
administration and uniformity of dosage. Dosage unit
form as used herein refers to physically discrete units
suited as unitary dosages for the mammalian subjects to
10 be treated; each unit containing a predetermined
quantity of active material calculated to produce the
desired therapeutic effect in association with the
required pharmaceutical carrier. The specification for
the novel dosage unit forms of the invention are
15 dictated by and directly dependent on (a) the unique
characteristics of the active material and the
particular therapeutic effect to be achieved, and (b)
the limitations inherent in the art of compounding such
an active material for the treatment of disease in
20 living subjects having a diseased condition in which
bodily health is impaired as herein disclosed in detail.

The principal active ingredient is compounded
for convenient and effect administration in effective
amounts with a suitable pharmaceutically acceptable
carrier in dosage unit form as hereinbefore disclosed.
25 A unit dosage form can, for example, contain the
principal active compound in amounts ranging from about
5 to about 1000 mg, with from about 5 to about 250 mg
being preferred. In the case of compositions containing
supplementary active ingredients, the dosages are
30 determined by reference to the usual dose and manner of
administration of the said ingredients.

1 For a better understanding of the present
invention together with other and further objects,
reference is made to the following description and
examples.

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Experimental Section - Compound Preparation

1 Melting points were determined in capillary
tubes on a Mel-Temp apparatus and are uncorrected.
Spectra were obtained as follows: CI mass spectra on a
5 Finnegan 4000 spectrometer; ¹H NMR spectra on a
Chemagnetics A-200 or Nicolet QE-300 or Varian VXR-500S
spectrometers with TMS as an internal standard in CDCl₃
or DMSO-d₆; IR spectra were obtained on a Beckman IR-33
spectrophotometer. Microanalyses were performed at the
10 Purdue Microanalysis Laboratory, and all values were
within ± 0.4% of the calculated composition. All
organic solvents were appropriately dried and/or
purified prior to use. Diethyl benzylphosphonate 7a,
aryl aldehydes 4a-t and 1 M solution of tetra-n-
15 butylammonium fluoride in THF were obtained from
commercial sources. Compounds 7b-c were prepared by the
reaction of the corresponding benzyl bromides and
triethyl phosphite. Phosphonium bromides 3a-b were
prepared by stirring a mixture of triphenyl phosphine
and the corresponding benzyl bromides in toluene.
20 Combretastatin A-4 and its trans isomer were obtained
from Prof. G. R. Pettit, Arizona State University.
Compound 1c was prepared as described previously.
Podophyllotoxin was obtained from Aldrich Chemical Co.,
and thiocolchicine was from Roussel-Uclaf. Preparative
25 silica gel tlc plates (200 micron) were purchased from
Analtech.

General procedure for the preparation of Z-
Stilbenes 5a-n and E-Stilbenes 6a-n. Sodium hydride (72
mg, 3 mmol) was added in portions to a well-stirred
30 suspension of phosphonium bromide 3a-b (2.0 mmol) and
aryl aldehyde (2.0 mmol) in benzene (20 mL) under argon

1 atmosphere at 0-5°C, and the mixture was allowed to warm
to room temperature. After an additional stirring for
16 h, excess sodium hydride was quenched by the addition
of methanol (1 mL). Solvents from the reaction mixture
were evaporated at reduced pressure, and the residue was
5 purified by preparative thin layer chromatography using
5% EtOAc in hexane as the eluent. Products 5d and 5l
were obtained as solids, and all the other cis stilbenes
were obtained as viscous oils.

10 (Z)-1-(4-Methoxyphenyl)-2-(3,4,5-trimethoxy-
phenyl)ethene (5a): 400 mg; 66%; oil: ¹H NMR (CDCl₃, 500
MHz) δ7.25 (d, J=9 Hz, 2 H), 6.80 (d, J=9 Hz, 2 H), 6.53
(d, J=12 Hz, 1 H), 6.51 (s, 2 H), 6.44 (d, J=12 Hz, 1
H), 3.84 (s, 3 H), 3.79 (s, 3 H), 3.69 (s, 6 H); CIMS
(isobutane) m/e 301 (MH⁺, 100). Anal. (C₁₈H₂₀O₄) C, H.

15 (Z)-1-(3-Methoxyphenyl)-2-(3,4,5-trimethoxy-
phenyl)ethene (5b): 410 mg; 69%; oil; ¹H NMR (CDCl₃, 200
MHz) δ7.18 (t, J=7.9 Hz, 1 H), 6.91-6.83 (m, 2 H), 6.78-
6.72 (m, 1 H), 6.58 (d, J=12.2 Hz, 1 H), 6.50 (d, J=12.2
Hz, 1 H), 6.49 (s, 2 H), 3.83 (s, 3 H), 3.70 (s, 3 H),
20 3.67 (s, 6 H); ¹³C NMR (CDCl₃, 50 MHz) δ159.94, 153.29,
139.63, 137.63, 132.84, 130.67, 130.22, 129.63, 121.79,
114.24, 113.46, 106.42, 61.06, 56.01, 55.26; CIMS
(isobutane) m/e 301 (MH⁺, 100). Anal. (C₁₈H₂₀O₄) C, H.

25 (Z)-1-(2-Methoxyphenyl)-2-(3,4,5-trimethoxy-
phenyl)ethene (5c): 440 mg; 73%; oil: ¹H NMR (CDCl₃, 500
MHz) δ7.27-7.20 (m, 2 H), 6.90 (d, J=8.4 Hz, 1 H), 6.82
(t, J=8.4 Hz, 1 H), 6.65 (d, J = 12.2 Hz, 1 H), 6.54 (d,
J=12.2 Hz, 1 H), 6.47 (s, 2 H), 3.84 (s, 3 H), 3.82 (s,
3 H), 3.63 (s, 6 H); CIMS (isobutane) m/e 301 (MH⁺,
30 100). Anal. (C₁₈H₂₀O₄) C, H.

1 (Z)-1-(4-Methoxyphenyl)-2-(2,3,4-trimethoxy-
phenyl)ethene (5d): 460 mg; 77%; mp 55-7°C; ¹H NMR
(CDCl₃, 200 MHz) δ7.19 (d, J=8.9 Hz, 2 H), 6.94 (d,
J=8.7 Hz, 1 H), 6.75 (d, J=8.9 Hz, 2 H), 6.52 (s, 2 H),
5 6.49 (d, J=8.7 Hz, 1 H), 3.90 (s, 3 H), 3.88 (s, 3 H),
3.84 (s, 3 H), 3.78 (s, 3 H); CIMS (isobutane) m/e 301
(MH⁺, 100). Anal. (C₁₈H₂₀O₄) C, H.

(Z)-1-(2-Chloro-4-methoxyphenyl)-2-(2,3,4-
trimethoxyphenyl)ethene (5e): 420 mg; 63%; oil; ¹H NMR
10 (CDCl₃, 500 MHz) δ7.21 (d, J=8.5 Hz, 1 H), 6.96 (d,
J=2.6 Hz, 1 H), 6.67 (dd, 1 H), 6.59 (d, J=12.1 Hz, 1
H), 6.57 (d, J=12.1 Hz, 1 H), 6.42 (s, 2 H), 3.82 (s, 3
H), 3.78 (s, 3 H), 3.66 (s, 6 H). Anal. (C₁₈H₁₉ClO₄) C,
H.

(Z)-1-Phenyl-2-(3,4,5-trimethoxyphenyl)ethene
15 (5f): 270 mg; 50%; oil; ¹H NMR (CDCl₃, 200 MHz) δ7.35-
7.25 (m, 5 H), 6.61 (d, J=12.2 Hz, 1 H), 6.50 (d, J=12.2
Hz, 1 H), 6.47 (s, 2 H), 3.83 (s, 3 H), 3.65 (s, 6 H);
¹³C NMR (CDCl₃, 50 MHz) δ153.27, 137.86, 137.12, 132.84,
130.48, 130.36, 129.28, 128.62, 127.51, 106.35, 61.09,
20 55.96; CIMS (isobutane) m/e 271 (MH⁺, 100). Anal.
(C₁₇H₁₈O₃) C, H.

(Z)-1-(4-Chlorophenyl)-2-(3,4,5-trimethoxy-
phenyl)ethene (5g): 7 mg; 50%; oil; ¹H NMR (CDCl₃, 200
MHz) δ7.23, (s, 4 H), 6.55 (d, J=12 Hz, H), 6.49 (d,
25 J=12 Hz, 1 H), 6.45 (s, 2 H), 3.84 (s, 3 H), 3.68 (s, 6
H); ¹³C NMR (CDCl₃, 50 MHz) δ153.43, 137.77, 136.17,
133.19, 132.53, 131.20, 130.74, 128.96, 128.75, 106.26,
61.10, 56.05; Anal. (C₁₇H₁₇ClO₃) C, H.

(Z)-1-(4-Bromophenyl)-2-(3,4,5-trimethoxy-
30 phenyl)ethene (5h): 363 mg; 52%; oil; ¹H NMR (CDCl₃, 200
MHz) δ7.38 (d, J=8.6 Hz, 2 H), 7.16 (d, J=8.6 Hz, 2 H),

1 6.56 (d, J=12.1 Hz, 1 H), 6.47 (d, J=12.1 Hz, 1 H), 6.44
(s, 2 H), 3.84 (s, 3 H), 3.68 (s, 6 H); ¹³C NMR (CDCl₃,
50 MHz) δ153.42, 137.77, 136.63, 132.49, 131.71, 131.28,
131.02, 128.98, 121.29, 106.25, 61.09, 56.05; CIMS
5 (isobutane) m/e 350 (93) 348 (MH⁺, 100). Anal.
(C₁₇H₁₇BrO₃) C, H.

(Z)-1-(4-Pyridyl)-2-(3,4,5-trimethoxyphenyl)-
ethene (5i): 277 mg; 51%; oil; ¹H NMR (CDCl₃, 500 MHz)
58.49 (d, J=6.0 Hz, 2 H), 7.18 (d, J=6.0 Hz, 2 H), 6.69
10 (d, J=12.2 Hz, 1 H), 6.48 (d, J=12.2 Hz, 1 H), 6.42 (s,
2 H), 3.84 (s, 3 H), 3.66 (s, 6H); CIMS (isobutane) m/e
272 (MH⁺, 100). Anal. (C₁₆H₁₇NO₃) C, H.

(Z)-1-(3-Pyridyl)-2-(3,4,5-trimethoxyphenyl)-
ethene (5j): 292 mg; 54%; oil; ¹H NMR (CDCl₃, 500 MHz)
58.53 (s, 1 H), 8.43 (d, J=4.8 Hz, 1 H), 7.60 (d, J=7.9
15 Hz, 1 H), 7.18 (dd, J₁=4.8 Hz, J₂=7.9 Hz, 1 H), 6.67
(d=12.2 Hz, 1 H), 6.53 (d, J=12.2 Hz, 1 H), 6.41 (s, 2
H), 3.84 (s, 3 H), 3.67 (s, 6 H); CIMS (isobutane) m/e
272 (MH⁺, 100). Anal. (C₁₆H₁₇NO₃) C, H.

(Z)-1-(2-Pyridyl)-2-(3,4,5-trimethoxyphenyl)-
ethene (5k): 351 mg; 65%; oil; ¹H NMR (CDCl₃, 500 MHz) d
8.64 (d, J=4.7 Hz, 1 H), 7.58-7.54 (dt, J₁=7.5 Hz, J₂=1.8
Hz, 1 H), 7.32-7.30 (m, 1 H), 7.17-7.15 (m, 2 H), 6.79
20 (d, J=12.4 Hz, 1 H), 6.58 (s, 2 H), 3.89 (s, 3 H), 3.74
(s, 6 H); CIMS (isobutane) m/e 272 (MH⁺, 100). Anal.
25 (C₁₆H₁₇NO₃) C, H.

(Z)-1-(4-Nitrophenyl)-2-(3,4,5-trimethoxy-
phenyl)ethene (5l): 170 mg; 27%; mp 140-142°C; ¹H NMR
(CDCl₃, 300 MHz) δ8.15 (d, J=8.6 Hz, 2 H), 7.56 (d,
J=8.6 Hz, 2 H), 7.05 (d, J=12 Hz, 1 H), 6.95 (d, J=12
30 Hz, 1 H), 6.71 (s, 2 H), 3.86 (s, 6 H), 3.82 (s, 3 H);

1 CIMS (isobutane) m/e 316 (MH^+ , 100). Anal. ($C_{17}H_{17}NO_5$) C, H.

(Z)-1-[(4-*t*-Butyldimethylsilyloxy)phenyl]-2-(3,4,5-trimethoxyphenyl)ethene (5m): 429 mg; 53%; oil; IR (Neat) 2980, 2960, 1610, 1580, 1520, 1470, 1420, 5 1360, 1330, 1270, 1140 cm^{-1} ; 1H NMR ($CDCl_3$, 300 MHz) δ 7.17 (d, $J=8.0$ Hz, 2 H), 6.73 (d, $J=8.0$ Hz, 2 H), 6.51 (s, 2 H), 6.41 (s, 2 H), 3.84 (s, 3 H), 3.79 (s, 6 H), 0.99 (s, 9 H), 0.14 (s, 6 H). Anal. ($C_{23}H_{32}O_4Si$) C, H.

(Z)-1-[4-(*N,N*-Dimethylamino)phenyl]-2-(3,4,5-trimethoxyphenyl)ethene (5n): 450 mg; 72%; oil; 1H NMR 10 ($CDCl_3$, 500 MHz) δ 7.22 (d, $J=8.9$ Hz, 2 H), 6.61 (d, $J=8.9$ Hz, 2 H), 6.58 (s, 2 H), 6.41 (d, $J=12.1$ Hz, 1 H), 6.34 (d, $J=12.1$ Hz, 1 H), 3.85 (s, 3 H), 3.72 (s, 6 H), 2.93 (s, 6 H); CIMS (isobutane) m/e 314 (MH^+ , 100). 15 Anal. ($C_{19}H_{23}NO_3$) C, H.

(E)-1-(4-Methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (6a): 67 mg; 11%; mp 152-5°C; 1H NMR 20 ($CDCl_3$, 500 MHz) δ 7.45 (d, $J=8.5$ Hz, 2 H), 6.97 (d, $J=16.0$ Hz, 1 H), 6.91 (d, $J=16.0$ Hz, 1 H), 6.90 (d, $J=8.5$ Hz, 2 H), 6.72 (s, 2 H), 3.87 (s, 6 H), 3.84 (s, 3 H), 3.82 (s, 3 H); CIMS (isobutane) m/e 301 MH^+ , 100). Anal. ($C_{18}H_{20}O_4$) C, H.

(E)-1-(4-Nitrophenyl)-2-(3,4,5-trimethoxyphenyl)ethene (6l): 280 mg; 44%; mp 192-4°C.

(E)-1-[(4-*t*-Butyldimethylsilyloxy)phenyl]-2-(3,4,5-trimethoxyphenyl)ethene (6m): 218 mg; 27%; oil; IR (Neat) 2980, 2960, 1605, 1585, 1520, 1470, 1420, 1340, 1320, 1270, 1170, 1130, 1010 cm^{-1} ; 1H NMR ($CDCl_3$, 300 MHz) δ 6.89 (d, $J=16.5$ Hz, 1 H), 6.81 (d, $J=16.5$ Hz, 1 H), 7.31 (d, $J=8.5$ Hz, 2 H), 6.76 (d, $J=8.5$ Hz, 2 H), 30

1 6.64 (s, 2 H), 3.84 (s, 3 H), 3.79 (s, 6 H), 0.92 (s, 9 H), 0.14 (s, 6 H). Anal. ($C_{23}H_{32}O_4Si$) C, H.

(E)-1-[4-(N,N-Dimethylamino)phenyl]-2-(3,4,5-trimethoxyphenyl)ethene (6n): 145 mg; 23%; mp 114-5°C; IR (KBr) 3000, 2980, 2940, 2860, 1600, 1580, 1520, 1340, 1240, 1120, 960 cm^{-1} ; 1H NMR (DMSO- d_6 , 500 MHz) δ 7.42 (d, J=8.85 Hz, 2 H), 7.10 (d, J=16.3 Hz, 1 H), 6.92 (d, J=16.3 Hz, 1 H), 6.86 (d, J=8.8 Hz, 2 H), 6.61 (s, 2 H), 3.83 (s, 6 H), 3.67 (s, 3 H), 2.94 (s, 6 H); CIMS (isobutane) m/e 314 (MH^+ , 100), 313 (72). Anal. $C_{19}H_{23}NO_3$) C, H.

(Z)-1-(4-Hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (5o): A solution of N-Bu₄NF in THF (1 M, 2 mL, 2 mmol) was added to a stirred solution of silyl ether 5 m (372 mg, 1 mmol) in THF (5 mL) at room temperature and the stirring was continued for 30 min. Solvent was removed at reduced pressure, the resulting residue was treated with 20 mL of water and the product was extracted with EtOAc (2 x 20 mL). The EtOAc solution was dried ($MgSO_4$), concentrated and the residue was crystallized from EtOAc/hexane to give 5 n (217 mg, 76%); mp 148-150°C; IR (KBr) 3440, 3020, 2940, 2840, 1610, 1580, 1510, 1420, 1330, 1230, 1160, 1120, 980, 790, 750 cm^{-1} ; 1H NMR ($CDCl_3$, 200 MHz) δ 7.40 (bs, 1 H), 7.24 (d, J=8.1 Hz, 2 H), 7.10 (d, J=8.1 Hz, 2 H), 6.60-6.30 (m, 4 H), 3.80 (s, 6 H), 3.76 (s, 3 H); CIMS (isobutane m/e 287 (MH^+ , 100). Anal. ($C_{17}H_{18}O_4$) C, H.

(E)-1-(4-Hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (6o): Using the same procedure described for 5o, compound 6o was prepared from 6 m in 1 mmol scale (228 mg, 80%); mp 188-90°C.

General procedure for the preparation of acetates (5p & 6p): A solution of n-Bu₄NF in THF (1 M, 2 mL, 2 mmol) was added to a solution of stilbenes 5m/6m (400 mg, 1 mmol) in THF (5 mL) and the mixture was stirred at 0°C. After 30 min., acetic anhydride (0.5 mL) was added, and the stirring was continued at room temperature for 24 h. Solvents were evaporated at reduced pressure, and the residue was mixed with water (50 mL). The product was extracted with ether (2 x 25 mL), and the ether solution was washed with water (2 x 100 mL). Evaporation of the solvents and purification of the crude product by preparative TLC using 40% ethyl acetate in hexanes as the eluent afforded the desired products.

(Z)-1-(4-Acetoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (5p): 93 mg; 28%; oil; ¹H NMR (CDCl₃, 500 MHz) δ 7.30 (d, J=8.3 Hz, 2 H), 6.98 (d, J=8.3 Hz, 2 H), 6.57 (d, J=12.1 Hz, 1 H), 6.47 (d, J=12.1 Hz, 1 H), 6.45 (s, 2 H), 3.83 (s, 3 H), 3.67 (s, 6 H), 2.29 (s, 3 H); CIMS (isobutane) m/e 329 (MH⁺, 100). Anal. (C₁₉H₂₀O₅) C, H.

(E)-1-(4-Acetoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (6p): 114 mg; 34%; oil; ¹H NMR (CDCl₃, 500 MHz) δ 7.51 (d, J=8.7 Hz, 2 H), 7.09 (d, J=8.7 Hz, 2 H), 6.99 (s, 2 H), 6.73 (s, 2 H), 3.92 (s, 6 H), 3.87 (s, 3 H), 2.31 (s, 3 H); CIMS (isobutane) m/e 329 (MH⁺, 100). Anal. C₁₉H₂₀O₅) C, H.

General procedure for the preparation of 6q-y: A solution of phosphonate esters 7a-c (12 mmol) in dry DMF (10 mL) was added to a magnetically stirred solution of NaOMe (0.65 g, 12 mmol) in dry DMF (10 mL) at 0°C and the solution was stirred for 30 min. A solution of

1 aldehyde 4d/4o-t (10 mmol) in dry DMF (10 mL) was added
at 0°C, and the reaction mixture was allowed to warm to
room temperature over a period of 1.5 h. The mixture
was heated at 95-100°C for 1 h and left overnight at
5 room temperature. The mixture was poured slowly onto
crushed ice, and the precipitated solid was filtered,
washed with water, dried and crystallized from EtOAc-
hexane.

(E)-1-(3,4-Dimethoxyphenyl)-2-phenylethene
10 (6q): 1.64 g; 68%; mp 106-8°C.
(E)-1-Phenyl-2-(2,3,4-trimethoxyphenyl)ethene
(6r): 2.34 g; 87%; mp 79-82°C; IR (KBr) 3020, 3000,
2980, 2940, 2840, 1600, 1510, 1470, 1420, 1300, 1260,
1230, 1090, 1030, 1000, 980 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz)
15 δ7.60-7.50 (m, 2 H), 7.40-7.20 (m, 5 H), 6.9 (d, J=60.5
Hz, 1 H), 6.70 (d, J=16.5 Hz, 1 H), 3.91 (s, 3 H), 3.90
(s, 3 H), 3.89 (s, 3 H); CIMS (isobutane) m/e 271 (MH⁺,
100). Anal. (C₁₇H₁₈O₃) C, H.

(E)-1-(4-Aminophenyl)-2-(3,4,5-trimethoxy-
phenyl)ethene (6z): Lithium aluminum hydride (76 mg, 2
20 mmol) was added to a solution of nitro stilbene 61 (270
mg, 0.87 mmol) in THF (25 mL), and the mixture was
stirred at room temperature for 12 h. Solvent was
evaporated at reduced pressure, and the residue was
decomposed by careful addition of ice water (20 mL)
25 containing 2 mL of glacial acetic acid. The red solid
formed was filtered and crystallized from CH₂Cl₂-ether to
give 6z (200 mg, 82%); mp 251-3°C; IR (KBr) 3440, 3400,
3000, 2920, 2820, 1600, 1580, 1510, 1340, 1240, 1130,
990, 950, 830 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ7.87 (d,
30 J=8.3 Hz, 2 H), 7.59 (d, J=8.3 Hz, 2 H), 7.08 (d, J=16.0
Hz, 1 H), 7.01 (d, J=16.0 Hz, 1 H), 6.71 (s, 2 H), 3.87

1 (s, 6 H), 3.82 (s, 3 H); CIMS (isobutane) m/e 286 (MH^+ , 100). Anal. ($C_{17}H_{19}NO_3$) C, H.

5 General procedure for the preparation of dihydrostilbenes 8. A solution of stilbene 5 and 6 (1 mmol) in EtOAc (25 mL) was hydrogenated at 40 psi in the presence of 10% Pd-C (30 mg) until the uptake of hydrogen ceased (4h). The solution was filtered and concentrated to obtain the dihydrostilbenes 8 almost as single components.

10 1-(4-Methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethane (8a): 280 mg; 93%; mp 73-5°C; 1H NMR ($CDCl_3$, 500 MHz) δ 7.10 (d, J=8.5 Hz, 2 H), 6.83 (d, J=8.5 Hz, 2 H), 6.36 (s, 2 H), 3.83 (s, 3 H), 3.82 (s, 6 H), 3.79 (s, 3 H), 2.80-2.90 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50. MHz) δ 158.53, 153.62, 138.16, 136.68, 134.23, 129.96, 15 114.22, 105.88, 61.16, 56.31, 55.52, 38.85, 37.33; CIMS (isobutane) m/e 303 (MH^+ , 100). Anal. ($C_{18}H_{22}O_4$) C, H.

20 1-[4-(Dimethylamino)phenyl]-2-(3,4,5-trimethoxyphenyl)ethane (8n): 265 mg; 84%; oil; 1H NMR ($CDCl_3$, 500 MHz) δ 7.08 (d, J=8.7 Hz, 2 H), 6.72 (d, J=8.7 Hz, 2 H), 6.38 (s, 2 H), 3.85 (s, 3 H), 3.83 (s, 6 H), 2.92 (s, 4 H), 2.82 (s, 6 H); CIMS (isobutane) m/e 316 (MH^+ , 100%). Anal. ($C_{19}H_{25}NO_3$) C, H.

25 1-(4-Aminophenyl)-2-(3,4,5-trimethoxyphenyl)ethane (8z): A solution of nitrostilbene 61 (250 mg, 0.8 mmol) in EtOAc (20 mL) was hydrogenated at 30 psi in the presence of 10% Pd-C (25 mg) at room temperature for 4 h, and the catalyst was filtered off. Evaporation of the solvent and crystallization of the residue from hexanes gave the amine 8z (180 mg, 80%); mp 30 84-5°C; IR (KBr) 3450, 3400, 3020, 2920, 2840, 1600, 1580, 1520, 1330, 1240, 1120, 980 cm^{-1} ; 1H NMR ($CDCl_3$,

1 300 MHz) d 6.98 (d, J=8.2 Hz, 2 H), 6.63 (d, J=8.2 Hz, 2 H), 6.63 (d, J=8.2 Hz, 2 H), 6.37 (s, 2 H), 3.83 (s, 9 H), 3.57 (bs, 2 H), 2.80 (s, 4 H); CIMS (isobutane) m/e 288 (MH⁺, 100). Anal. (C₁₇H₂₁NO₃) C, H.

5 1-(4-Acetamidophenyl)-2-(3,4,5-trimethoxy-phenyl)ethane (8 m): The amine 8z (0.574 g, 2 mmol) was dissolved in dry benzene (10 mL) containing triethylamine (0.5 mL) and cooled to 0°C. Acetyl chloride (320 mg, 4 mmol) was added dropwise, and the solution was stirred for 30 min. The contents were
10 poured into ice cold water, and the mixture was extracted with ether (25 mL). The organic layer was washed with water, 5% sodiumbicarbonate solution, and dried (MgSO₄) and the solvent was evaporated. The
15 residue was crystallized from EtOAc-hexane (0.52 g, 79%); mp 112-4 °C; IR (KBr) 3450, 3000, 2930, 2840, 1670, 1600, 1580, 1510, 1340, 1120 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 7.52 (bs, 1 H), 7.42 (d, J=8.4 Hz, 2 H), 7.11 (d, J=8.4 Hz, 2 H), 6.36 (s, 2 H), 3.82, (s, 3 H), 3.81 (s, 6H), 2.85 (s, 4 H), 2.14 (s, 3 H); CIMS (isobutane)
20 m/e 330 (MH⁺, 100). Anal. (C₁₉H₂₃NO₄) C, H.

General procedure for preparation of
Benzamides 11a-f. Aroyl chloride 9a-d (20 mmol) was added to a stirred solution of substituted aniline 10a-c
25 (20 mmol) in pyridine (50 mL) at room temperature, and the reaction mixture was stirred for 4 h and poured into a mixture of ice (400 g) and hydrochloric acid (100 mL). The precipitated product was filtered, washed with water, dried and recrystallized from CHCl₃-hexane.

3,4,5-Trimethoxy-N-(4-methoxyphenyl)benzamide
30 (11a): 5.83 g; 92%; mp 160-161°C; ¹H NMR (CDCl₃, 500 MHz) δ 8.22 (bs, 1 H), 7.50 (d, J=8.1 Hz, 2 H), 7.03 (s,

1 2 H), 6.83 (d, J=8.1 Hz, 2 H), 3.85 (s, 3 H), 3.80 (s, 6 H), 3.77 (s, 3 H); CIMS (isobutane) m/e 318 (MH⁺, 100).

4-Methoxy-N-(3,4,5-trimethoxyphenyl)benzamide (11c): 5.60 g; 88%; mp 159-160°C; IR (KBr) 3300, 2980, 2940 1650, 1605, 1515, 1455, 1420, 1340, 1270, 1220, 5 1020, 1000 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ8.18 (bs, 1 H), 7.60 (d, J=8.0 Hz, 2 H), 6.90 (s, 2 H), 6.88 (d, J=8.0 Hz, 2 H), 3.92 (s, 3 H), 3.80 (s, 6 H), 3.76 (s, 3 H); CIMS (isobutane) m/e 318 (MH⁺, 100). Anal. (C₁₇H₁₉NO₅) C, 10 H.

10 General procedure for preparation of N-benzylanilines 12a-f. A solution of benzamide 11a-f (5 mmol) in THF (50 mL) was added to a well-stirred suspension of lithium aluminum hydride (0.285 g, 7.5 mmol) in dry THF (10 mL) at 0°C under nitrogen 15 atmosphere, and the reaction mixture was allowed to warm to room temperature. After 4 h, the reaction mixture was poured onto ice (200 g), and the mixture was extracted with ether (3 x 20 mL). The combined extracts 20 were washed with water and dried (K₂CO₃). Evaporation of ether from the solution afforded amines 12a-f almost as single products. Analytical samples of solid products were prepared by crystallization from ether-hexane, and liquids were purified by preparative thin-layer chromatography using 2% methanol in CHCl₃ as eluent.

25 3,4,5-Trimethoxy-N-(4-methoxyphenyl)-benzylamine (12a): 1.42 g; 94%; mp 73-4°C; IR (KBr) 3400, 2990, 2920, 2220, 1600, 1510, 1460, 1420, 1330, 1260, 1230, 1120, 1110, 1030, 1000 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ6.78 (d, J=8.6 Hz, 2 H), 6.62 (d, J=8.6 Hz, 2 30 H), 6.61 (s, 2 H), 4.21 (s, 2 H), 3.86 (bs, 1 H), 3.84 (s, 9 H), 3.74 (s, 3 H); ¹³C NMR (CDCl₃, 50 MHz) δ153.98,

1 152.88, 143.03, 137.50, 136.04, 115.37, 114.66, 104.77,
61.18, 56.39, 56.08, 50.00; CIMS (isobutane) m/e 304
(MH⁺, 100). Anal. (C₁₇H₂₁NO₄) C, H.

4-Methoxy-N-(3,4,5-trimethoxyphenyl)-
benzylamine (12c): 1.42 g; 94%; mp 77-8°C; IR (KBr)
5 3380, 2980, 2960, 2940, 2820, 1605, 1580, 1520, 1460,
1440, 1255, 1225, 1130, 1110, 1010, 990 cm⁻¹; ¹H NMR
(CDCl₃, 500 MHz) δ 7.29 (d, J=8.6 Hz, 2 H), 6.88 (d,
J=8.6 Hz, 2 H), 5.87 (s, 2 H), 4.22 (s, 2 H), 3.82 (bs,
1 H), 3.80 (s, 3 H), 3.79 (s, 6 H), 3.76 (s, 3 H); CIMS
10 (isobutane) m/e 304 (MH⁺, 100). Anal. (C₁₇H₂₁NO₄) C, H.

4-Benzyloxy-3,5-dimethoxybenzaldehyde (13j).
A mixture of syringaldehyde (3.64 g, 20 mmol), benzyl
chloride (2.52 g 20 mmol), NaI (2 g) and potassium
carbonate (2.76 g, 20 mmol) in anhydrous acetone (60 mL)
15 were refluxed for 5 h and cooled to room temperature.
The solid materials were removed by filtration, the
filtrate was concentrated and the residue was purified
by chromatography on silica gel (230-400 mesh, 50 g)
using 5% EtOAc in hexane as the eluent to obtain 13j
20 (4.3 g, 79%); mp 62-63°C.

4-(t-Butyldimethylsilyloxy)-3,5-dimethoxyben-
zaldehyde (13k). To a well-stirred solution of
syringaldehyde (3.64 g, 20 mmol) and N,N-diisopropyl-
ethylamine (4.87 g, 30 mmol) in dry DMF (30 mL) at 0°C,
25 t-butyldimethylsilyl chloride (3 g, 20 mmol) was added,
and stirring was continued for 2 h at 0°C and at room
temperature for 10 h. The mixture was poured into
icewater (500 mL), and the product was extracted with
hexane (3 x 70 mL). The combined hexane extracts were
30 washed with water (4 x 70 mL) and dried Na₂SO₄.
Evaporation of solvents gave compound 4k as a white

1 crystalline solid (5.17 g, 87%). An analytical sample
was prepared by recrystallization from anhydrous
ethanol. mp 70-71°C; ¹H NMR (CDCl₃, 200 MHz) δ 9.81 (s, 1
H), 7.09 (s, 2 H), 3.85 (s, 6 H), 0.99 (s, 9 H), 0.14
5 (s, 6 H). Anal. (C₁₅H₂₄O₄Si) C, H.

The following compounds were prepared in
accordance with the procedure described herein. More
specifically, heating 3,4,5-trimethoxybenzaldehyde with
p-substituted anilines 107a-g in refluxing toluene
10 provided the Schiff bases 108a-g. Reduction of the
imines 108a-g with sodium borohydride in ethanol at
reflux gave the amines 109a-g, which were converted to
the corresponding hydrochloride salts 110a-g with HCl
gas in ether. All of the hydrochloride salts 110a-g
15 were isolated as stable, crystalline solids.

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Scheme

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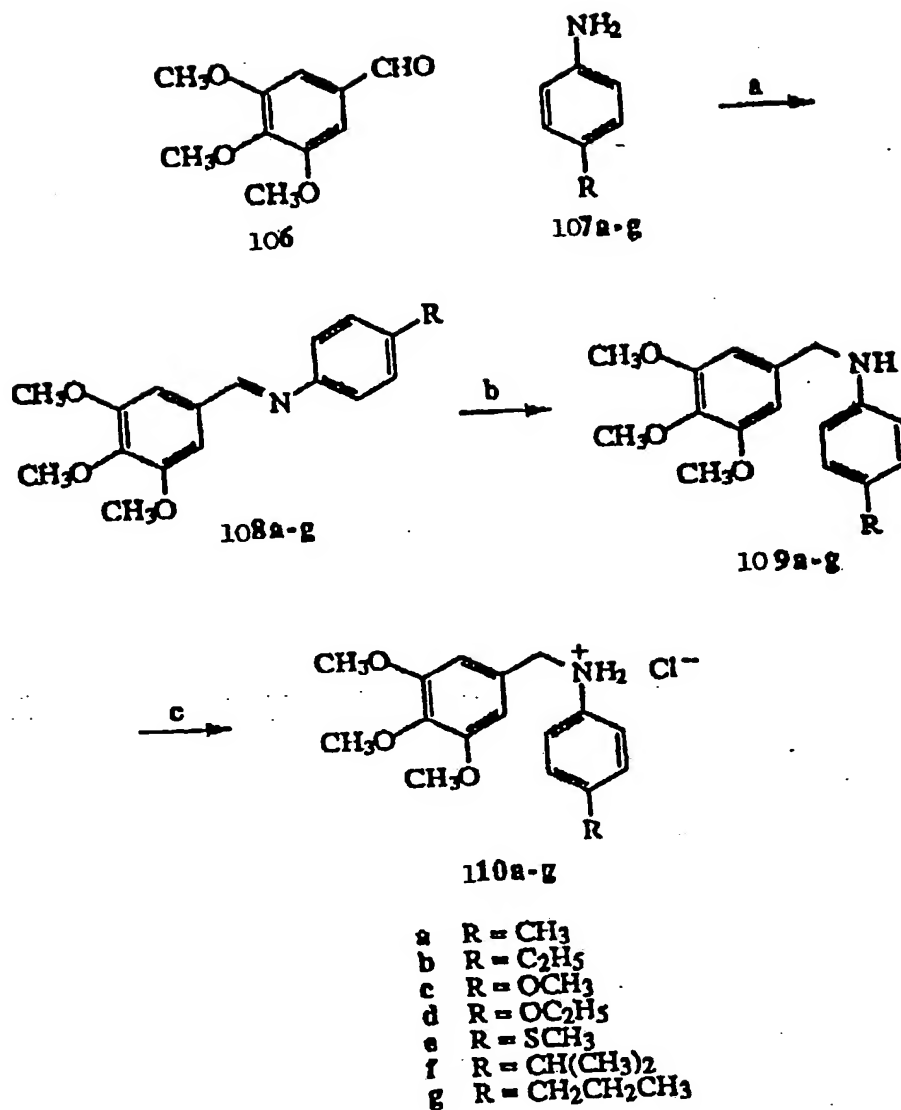
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^aToluene, reflux (3 h). ^bNaBH₄, ethanol, reflux (2 h). ^cHCl, ether, 0-5 °C (30 min).

1 4-Methyl-N-(3,4,5-trimethoxybenzylidene)
aniline (108a). A mixture of compound 106 (6.0 g, 98%,
31.0 mmol) and 107a (3.21 g, 30 mmol) in ethanol (150
mL) was heated at reflux under argon for 3h. After
5 evaporation of the solvent, the residual white solid was
recrystallized from ethyl acetate and hexane to give
108(a) (7.05 g, 82.4%) as white crystals: mp 74-6 °C.
¹H NMR (200 MHz, CDCl₃) δ 8.36 (s, 1 H), 7.20 (d, J=8 Hz,
2 H), 7.16 (s, 2 H), 7.15 (d, J=8 Hz, 2 H), 3.95 (s, 6
H), 3.92 (s, 3 H), 2.36 (s, 3 H). EIMS m/e 285 (M⁺,
100).

 4-Ethyl-N-(3,4,5-trimethoxybenzylidene)aniline
(108b). A solution of 106 (6.0 g, 98%, 30 mmol) and
107b (3.63 g, 30 mmol) in ethanol (150 mL) was heated at
15 reflux under argon for 3 h. The solvent was evaporated
and the residual oil was subjected to flash
chromatography (silica gel, 230-400 mesh, ether:hexane,
4:6 by volume) to give 108b (8.1 g, 90.3%) as an oil.
¹H NMR (200 MHz, CDCl₃) δ 8.36 (s, 1 H), 7.23 (d, J=8 Hz,
2 H), 7.16 (s, 2 H), 7.15 (d, J=8 Hz, 2 H), 3.94 (s,
20 6H), 3.91 (s, 3 H), 2.67 (q, J=8 Hz, 2 H), 1.26 (t, J=8
Hz, 3 H). EIMS m/e 299 (M⁺, 100).

 4-Methoxy-N-(3,4,5-trimethoxybenzylidene)-
aniline (108c). A mixture of 3,4,5-trimethoxybenzaldehyde 106 (19.6 g, 100 mmol) and 4-methoxyaniline (107c)
25 (12.3 g, 100 mmol) in ethanol (100 mL) was heated at
reflux under argon for 3 h. About half of the solvent
was evaporated and the residual solution was filtered
through a glass wool pad. The filtrate was left at room
temperature overnight to give the crystalline (108c)
30 (28.2 g, 93.7%): mp 78-86°C. ¹H NMR (200 MHz, CDCl₃)
δ 8.36 (s, 1 H), 7.23 (d, J=8 Hz, 2 H), 7.15 (s, 2 H),

1 6.93 (d, J=8 Hz, 2 H), 3.94 (s, 6 H), 3.91 (s, 3 H),
3.83 (s, 3 H). CIMS (isobutane) m/e 302 (MH⁺, 100).
Anal. (C₁₇H₁₉NO₄)C, H, N.

5 4-Ethoxy-N-(3,4,5-trimethoxybenzylidene)-
aniline (108d). From 3,4,5-trimethoxybenzaldehyde 106
(6.0 g, 30 mmol) and 4-ethoxyaniline 107d (4.1 g, 30
mmol), a similar procedure as described for 108a (5.9 g,
97.4%) as yellow crystals: mp 75-7°C after
recrystallization from ethanol. ¹H NMR (200 MHz, CDCl₃)
10 68.37 (s, 1 H), 7.21 (d, J=8 Hz, 2 H), 7.14 (s, 2 H),
6.91 (d, J=8 Hz, 2 H), 4.05 (q, J=6 Hz, 2 H), 3.94 (s,
6H), 3.91 (s, 3 H), 1.43 (t, J=6 Hz, 3 H). EIMS m/e 315
(M⁺, 93).

15 4-Methylthio-N-(3,4,5-trimethoxybenzylidene)-
aniline (108e). From compounds 107e (5.0g, 98%, 35.2
mmol) and 106 (7.04g, 98%, 35.2 mmol), a similar
procedure, as described for 108a gave 108e (11.0 g,
98.2%) as yellow solid. The analytical sample was
obtained by preparative TLC (ether:hexane, 1:2 by
volume, precoated silica TLC plate, 1000 microns):
20 mp 86-88°C. ¹H NMR (200 MHz, DMSO-d₆) 68.54 (s, 1 H),
7.31 (d, J=8 Hz, 2 H), 7.23 (d, J=8 Hz, 2 H), 7.26
(s, 2 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.73 (s, 3 H),
2.49 (s, 3 H), 2.49 (s, 3 H). EIMS m/e 317 (M⁺, 100).

25 4-Isopropyl-N-(3,4,5-trimethoxybenzylidene)-
aniline (108f). From compounds 107f (4.2g, 99%, 31.0
mmol) and 106 (6.0g, 98%, 31.0 mmol), a similar
procedure as described for 108a gave 108f (8.2 g, 84.5%)
as a yellow solid: mp 68-70. ¹H NMR (200 MHz, CDCl₃)
30 68.37 (s, 1 H), 7.25 (d, J=8 Hz, 2 H), 7.16 (d, J=8 Hz,
2 H), 7.16 (s, 2 H), 3.94 (s, 6 H), 3.91 (s, 3 H), 2.93

1 (sextet, $J=8$ Hz, 1 H), 1.27 (d, $J=8$ Hz, 6 H). EIMS m/e
313 (M^+ , 100).

5 4-n-Propyl-N-(3,4,5-trimethoxybenzylidene)-
aniline (108g). From compounds 107g (4.2g, 99%, 31.0
mmol) and 106 (6.0 g, 98%, 31.0 mmol), a similar
procedure as described for 108a gave 108g (8.5 g, 87.6%)
as a thick oil. 1H NMR (200 MHz, $CDCl_3$) δ 8.36 (s, 1 H),
7.20 (d, $J=8$ Hz, 2 H), 7.16 (s, 2 H), 7.14 (d, $J=8$ Hz, 2
H), 3.93 (s, 6 H), 3.91 (s, 3 H), 2.60 (t, $J=8$ Hz, 2 H),
10 1.64 (sextet, $J=8$ Hz, 2 H), 0.95 (t, $J=8$ Hz, 3 H). EIMS
(M^+ 100).

15 4-Methyl-N-(3,4,5-trimethoxybenzyl)aniline
(109a). To a solution of (108a) (6.0 g, 21.1 mmol) in
ethanol (100 mL) was added $NaBH_4$ (4.06 g, 98%, 105 mmol)
in portions. The reaction mixture was stirred at reflux
under argon for 2h. The solvent was removed under
reduced pressure. Saturated aqueous NaCl (30 mL) was
added to the residue and the mixture extracted with
20 ether (100, 40 and 40 mL). The combined ether layer was
washed with saturated NaCl solution (30 mL), and dried
over anhydrous Na_2SO_4 . Evaporation of the filtrate gave
109a (5.6 g, 92.7%) as white crystals: mp 94-6°C after
recrystallization from ethanol. 1H NMR (200 MHz, $CDCl_3$)
25 δ 7.00 (d, $J=8$ Hz, 2 H), 6.61 (s, 2 H), 6.58 (d, $J=8$ Hz,
2 H), 4.23 (s, 2 H), 3.84 (s, 9 H), 2.24 (s, 3 H). CIMS
(isobutane) m/e 288 (MH^+ 76).

30 4-Ethyl-N-(3,4,5-trimethoxybenzyl)aniline
(109b). From 108b (7.0 g, 23.4 mmol) and $NaBH_4$ (4.4 g,
117 mmol), a similar procedure as described for 109a
gave 109b (5.4 g, 76.6%) as white crystals: mp 64-6°C
after recrystallization from ethanol. 1H NMR (200 MHz,

1 CDCl_3) δ 7.03 (d, $J=8$ Hz, 2 H), 6.61 (s, 2 H), 6.62 (d, $J=8$ Hz, 2 H), 4.24 (s, 2 H), 3.84 (s, 9 H) 2.55 (q, $J=8$ Hz, 2 H), 1.19 (t, $J=8$ Hz, 3 H). EIMS m/e 301 (M^+ , 34).

5 4-Methoxy-N-(3,4,5-trimethoxybenzyl)aniline (109c). From 108c (10.8 g, 35.8 mmol) and NaBH_4 (6.8 g, 179 mmol), a similar procedure as described for 109a gave 109c (10.1 g, 93.5%) as pale purple crystals. ^1H NMR (200 MHz, CDCl_3) δ 6.79 (d, $J=8$ Hz, 2 H), 6.62 (d, $J=8$ Hz, 2 H), 6.61 (s, 2 H), 4.21 (s, 2 H), 3.84 (s, 9H), 3.74 (s, 3 H). CIMS (isobutane) m/e 304 (MH^+ , 20).

10 4-Ethoxy-N-(3,4,5-trimethoxybenzyl)aniline (109d). From the imine 108d (5.6 g, 17.8 mmol) and NaBH_4 (3.4 g, 88 mmol), a similar procedure as described for 109a gave 109d (4.6g, 81.9%) as white crystals: mp 76-8°C after recrystallization from ethanol. ^1H NMR (200 MHz, CDCl_3) δ 6.78 (d, $J=8$ Hz, 2 H), 6.62 (d, $J=8$ Hz, 2 H), 6.61 (s, 2 H), 4.21 (s, 2 H), 3.96 (q, $J=6$ Hz, 2 Hz), 3.84 (s, 9 H), 1.37 (t, $J=6$ Hz, 3 H). CIMS (isobutane) m/e 318 (MH^+ , 27).

20 4-Methylthio-N-(3,4,5-trimethoxybenzyl)aniline (109e). From 108e (11.0 g, 35.0 mmol) and NaBH_4 (6.6 g, 175 mmol), a similar procedure as described in 109a gave 109e (10.6 g, 94.9%) as an oil: ^1H NMR (200 MHz, $\text{DMSO}-d_6$) δ 7.07 (d, $J=8$ Hz, 2 H), 6.67 (s, 2 H), 6.57 (d, $J=8$ Hz, 2 H), 6.23 (t, $J=6$ Hz, 1 H), 4.10, (d, $J=6$ Hz, 2 H), 25 3.73 (s, 6 H), 3.62 (s, 3 H), 2.31 (s, 3 H). EIMS m/e 319 (M^+ , 69).

30 4-Isopropyl-N-(3,4,5-trimethoxybenzyl)aniline (109f). From 108f (8.2 g, 26.0 mmol), a similar procedure as described for 109a gave 109f (7.4 g, 89.8%) as an oil. ^1H NMR (200 MHz, CDCl_3) δ 7.06 (d, $J=8$ Hz, 2 H), 6.61 (d, $J=8$ Hz, 2 H), 6.61 (s, 2 H), 4.24 (s, 2 H),

- 1 3.84 (s, 9 H), 2.81 (h, J=8 Hz, 1 H, 1.21 (d, J=8 Hz, 6 H). EIMS 315 (M^+ , 100).

5 4-n-Propyl-N-(3,4,5-trimethoxybenzyl)aniline (109g). From 108g (8.5 g, 26.9 mmol), a similar procedure as described for 109a gave 109g (6.0 g, 70.3%) as an oil. ^1H NMR (200 MHz, CDCl_3) δ 7.00 (d, J=8 Hz, 2 H), 6.61 (s, 2 H), 6.60 (d, J=8 Hz, 2 H), 4.23 (s, 2 H), 3.84 (s, 9 H), 2.84 (t, J=8 Hz, 2 H), 1.60 (sextet, J=8 Hz, 2 H), 0.92 (t, J=8 Hz, 3 H). EIMS m/e 315 (M^+ , 93).

10 4-Methyl-N-(3,4,5-trimethoxybenzyl)aniline Hydrochloride (110a). A solution of 109a (3.9g, 13.6 mmol) in ether (150 mL) was treated with HCl gas at 0-5°C with stirring for about 0.5h. Collection of the resulting pale purple crystals and recrystallization from ethanol and methanol gave 109a (3.6 g, 81.8%) as
15 tiny white crystals: mp 162-4°C after recrystallization from ethanol. ^1H NMR (200 MHz, CDCl_3) δ 7.21 (d, J=2 H), 7.09 (d, J=8 Hz, 2 H), 6.63 (s, 2 H), 4.26 (s, 2 H), 3.77 (s, 6 H), 3.76 (s, 3 H), 2.30 (s, 3 H). Anal. ($\text{C}_{17}\text{H}_{22}\text{ClNO}_3$) C, H, N.

20 4-Ethyl-N-(3,4,5-trimethoxybenzyl)aniline Hydrochloride (110b). From 109b (4.0 g, 13.2 mmol), a similar procedure as described in 110a gave 110b (3.17 g, 70.7%), as yellow crystals: mp 155-7°C after
25 recrystallization from ethanol and methanol. ^1H NMR (200 MHz, CDCl_3) δ 7.20 (s, br, 4 H), 6.86 (s, 2 H), 4.34 (s, 2 H), 3.72 (s, 6 H), 3.62 (s, 3 H), 2.55 (q, J=8 Hz, 2 H), 1.13 (t, J=8 Hz, 3 H). Anal. ($\text{C}_{18}\text{H}_{24}\text{ClNO}_3$).

30 4-Methoxy-N-(3,4,5-trimethoxybenzyl)aniline Hydrochloride (110c). From 109c (9.0 g, 29.7 mmol), a similar procedure as described for 110a gave 110c (8.14 g, 80.7%) as tiny white crystals: mp 182-4°C. ^1H NMR

1 (200 MHz, DMSO- d_6) δ 7.36 (d, J=8 Hz, 2 H), 6.98 (d, J=8 Hz, 2 H), 6.62 (s, 2 H), 4.36 (s, 2 H), 3.74 (s, 9 H), 3.63 (s, 3 H). Anal. ($C_{17}H_{22}ClNO_4 \cdot \frac{1}{2}H_2O$) C, H, N.

5 4-Ethoxy-N-(3,4,5-trimethoxybenzyl)aniline Hydrochloride (110d). From 109d (4.0 g, 12.6 mmol), a similar procedure as described for 110a gave 109d (3.4 g, 76.2%) as white crystals: mp 170-2°C after recrystallization from ethanol and methanol. 1H NMR (200 MHz $CDCl_3$) δ 7.22 (d, J=8 Hz, 2 H), 6.57 (d, J=8 Hz, 2 H) 6.64 (s, 2 H), 4.25 (s, br, 2 H), 3.95 (q, J=6 Hz, 2 H), 3.79 (s, 6 H), 3.77 (s, 3 H), 1.38 (t, J=6 Hz, 3 H). Anal. ($C_{18}H_{24}ClNO_4$) C, H, N.

15 4-Methylthio-N-(3,4,5-trimethoxybenzyl)aniline Hydrochloride (110e). From 109e (3.0 g, 9.4 mmol), a similar procedure as described for 110a gave 110e (1.80 g, 53.9%) as yellow crystals: mp 194-6°C after recrystallization from ethanol:methanol:water. 1H NMR (200 MHz, DMSO- d_6) δ 7.23 (d, J=8 Hz, 2 H), 7.07 (d, J=8 Hz, 2 H), 6.83 (s, 2 H), 4.30 (s, 2 H), 3.73 (s, 6 H), 20 3.62 (s, 3 H), 3.62 (s, 3 H), 2.40 (s, 3 H). Anal. ($C_{17}H_{22}ClNO_3S$) C, H, N.

25 4-Isopropyl-N-(3,4,5-trimethoxybenzyl)aniline Hydrochloride (110f). From 109f (6.0 g, 18.9 mmol), a similar procedure as described for 110a gave 110f (4.4 g, 65.9%), as yellow crystals: mp 160-2°C after recrystallization from methanol:ethanol:water. 1H NMR (200 MHz, $CDCl_3$) δ 7.35 (d, J=8 Hz, 2 H), 7.29 (d, J=8 Hz, 2 H), 6.92 (s, 2 H), 4.37 (s, 2 H), 3.73 (s, 6 H), 3.63 (s, 3 H), 2.88 (h, J=6 Hz, 1 H), 1.17 (d, J=6 Hz, 6 30 H). Anal. ($C_{19}H_{26}ClNO_3$) C, H, N.

- 1 4-n-Propyl-N-(3,4,5-trimethoxybenzyl)aniline
Hydrochloride (110g). From 109g (6.0 g, 19.0 mmol), a
similar procedure as described for 110a gave 110g (5.5
g, 82.5%) as yellow crystals, mp 118-20°C after
recrystallization from ethyl acetate:methanol:hexane.
- 5 ¹H NMR (200 MHz, CDCl₃) 67.21 (d, J=8 Hz, 2 H), 7.08 (d,
J=8 Hz, 2 H), 6.58 (s, 2 H), 4.29 (s, 2 H), 3.78 (s, 3
H), 3.74 (s, 6 H), 3.52 (t, J = 8 Hz, 2 H), 1.56
(sextet, J=8 Hz, 2 H), 0.86 (t, J=8 Hz, 3 H). Anal.
(C₁₉H₂₆ClNO₃) C, H, N.
- 10 4-Methoxy-N-(3,4,5-trimethoxybenzylidene)-
aniline (108c). Anal. calcd for C₁₇H₁₉NO₄: C, 67.76; H,
6.35; N, 4.65. Found: C, 68.11; H, 6.28; N, 4.54.
- 4-Methyl-N-(3,4,5-trimethoxybenzyl)aniline
Hydrochloride (110a). Anal. calcd for C₁₇H₂₂ClNO₃: C,
15 63.06; H, 7.01; N, 4.33. Found: C, 62.92; H, 7.15; N,
4.37.
- 4-Ethyl-N-(3,4,5-trimethoxybenzyl)aniline
Hydrochloride (110b). Anal. calcd for C₁₈H₂₄ClNO₃: C,
20 63.99; H, 7.16; N, 4.15. Found: C, 63.96; H, 7.24; N,
3.90.
- 4-Methoxy-N-(3,4,5-trimethoxybenzyl)aniline
Hydrochloride (110c). Anal. calcd for C₁₇H₂₂ClNO₄·½H₂O:
C, 58.53; H, 6.64; N, 4.02. Found: C, 58.52; H, 6.31;
N, 3.89.
- 25 4-Ethoxy-N-(3,4,5-trimethoxybenzyl)aniline
Hydrochloride (110d). Anal. calcd for C₁₈H₂₄ClNO₄:
C, 61.10; H, 6.84; N, 3.96. Found: C, 61.27; H, 6.91;
N, 3.68.
- 4-Methylthio-N-(3,4,5-trimethoxybenzyl)aniline
30 Hydrochloride (110e). Anal. calcd for C₁₇H₂₂ClNO₃S: C,

1 57.37; H, 6.23; N, 3.94. Found: C, 57.19; H, 6.33; N, 3.95.

5 4-Isopropyl-N-(3,4,5-trimethoxybenzyl)aniline Hydrochloride (110f). Anal. calcd for $C_{19}H_{26}ClNO_3$: C, 64.86; H, 7.44; N, 3.98. Found: C, 64.75; H, 7.51; N, 3.95.

10 4-n-Propyl-N-(3,4,5-trimethoxybenzyl)aniline Hydrochloride (110g). Anal. calcd for $C_{19}H_{26}ClNO_3$: C, 64.86; H, 7.44; N, 3.98, Found: C, 64.59; H, 7.61; N, 3.94.

15 General procedure for the preparation of Stilbenes 15a-k. Sodium hydride (0.2 g, 4 mmol) was added to a well-stirred suspension of the phosphonium bromide 14a-b (2 mmol) and the aldehyde 13a-k (2 mmol) in THF (30 mL), and the mixture was stirred at room temperature for 24 h. The mixture was cooled to 0°C, and the excess sodium hydride was quenched by careful addition of methanol (5 mL). Solvents were removed at reduced pressure, and the residue was subjected to preparative thin-layer chromatography on silica gel using 20% EtOAc in hexane as the eluent to get the Z and E isomers in pure form.

25 (Z)-1-(4-Ethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (15a): 313 mg; 44%; oil; 1H NMR ($CDCl_3$, 200 MHz) δ 7.23 d, J=8.8 Hz, 2 H), 6.78 (d, J=8.8 Hz, 2 H), 6.52 (d, J=12.1 Hz, 1 H), 6.51 (s, 2 H), 6.41 (d, J=12.1 Hz, 1 H), 4.01 (q, J=7.0 Hz, 2 H), 3.84 (s, 3 H), 3.69 (s, 6 H), 1.39 (t, J=7.0 Hz, 3 H); CIMS (isobutane) m/e 315 (MH^+ , 100). Anal. ($C_{19}H_{22}O_4$) C, H.

30 (Z)-1-(4-n-Propoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-thene (15b): 346 mg; 53%; oil; 1H NMR ($CDCl_3$, 200 MHz) δ 7.23 (d, J=8.8 Hz, 2 H), 6.78 d, J=8.8

- 1 Hz, 2 H) 6.52 (s, 2 H), 6.52 (d J=12.2 Hz, 1 H), 6.41
(d, J=12.2 Hz, 1 H) (d, J=12.2 Hz, 1 H), 3.88 (t, J=6.6
Hz, 2 H), 3.84 (s, 3 H), 3.69 (s, 6 H), 1.79 (sextet,
J=6.6 Hz, 2 H), 1.02 (t, J=6.6 Hz, 3 H); CIMS
5 (isobutane) m/e 329 MH⁺, 100). Anal. (C₂₀H₂₄O₄) C, H.
(Z)-1-(4-Methylthiophenyl)-2-(3,4,5-
trimethoxyphenyl)ethene (15c): 319 mg; 51%; oil; ¹H NMR
(CDCl₃, 200 MHz) δ 7.23 (d, J=8.4 Hz, 2 H), 7.13 (d,
J=8.4 Hz, 2 H), 6.50 (bs, 2 H), 6.49 (s, 2 H), 3.84 (s,
10 3 H), 3.69 (s, 6 H), 2.46 (s, 3 H); CIMS (isobutane) m/e
317 (MH⁺, 100). Anal. (C₁₈H₂₀O₃S) C, H.
(Z)-(4-Methylphenyl)-2-(3,4,5-trimethoxy-
phenyl)ethene (15d): 294 mg; 50%; oil; ¹H NMR (CDCl₃,
200 MHz) δ 7.20 (d, J=8.0 Hz, 2 H), 7.07 (d, J=8.0 Hz, 2
H), 6.56 (d, J=12.2 Hz, 1 H), 6.49 (s, 2 H), 6.45 (d,
15 J=12.2 Hz, 1 H), 3.83 (s, 3 H), 3.67 (s, 6 H), 2.31 (s,
3 H); ¹³C NMR (CDCl₃, 50 MHz) δ 153.28, 137.56, 137.30,
134.77, 133.14, 130.35, 129.82, 129.22, 106.31, 61.09,
55.99, 21.27; CIMS (isobutane) m/e 285 (MH⁺, 100).
Anal. (C₁₈H₂₀O₃) C, H.
20 (Z)-(4-Ethylphenyl)-2-(3,4,5-trimethoxy-
phenyl)ethene (15e): 321 mg; 54%; oil; ¹H NMR (CDCl₃,
200 MHz) δ 7.21 (d, J=8.1 Hz, 2 H), 7.00 (d, J=8.1 Hz, 2
H), 6.57 (d, J=12.1 Hz, 1 H), 6.48 (s, 2 H), 6.46 (d,
J=12.1 Hz, 1 H), 3.84 (s, 3 H), 3.66 (s, 6 H), 2.61 (q,
25 J=7.4 Hz, 2 H), 1.20 (t, J=7.4 Hz, 3 H); CIMS
(isobutane) m/e 299 (MH⁺, 100). Anal. (C₁₉H₂₂O₃) C, H.
(Z)-[4-(2-Propyl)phenyl]-2-(3,4,5-
trimethoxyphenyl)ethene (15f): 340 mg; 55%; oil; ¹H NMR
(CDCl₃, 200 MHz) δ 7.23 (d, J=8.2 Hz, 2 H); 7.13 (d,
30 J=8.2 Hz, 2 H), 6.60 (d, J=12.2 Hz, 1 H), 6.46 (s, 2 H),
6.46 (d, J=12.2 Hz, 1 H), 3.83 (s, 3 H), 3.65 (s, 6 H),

1 2.88 (sextet, $J=7.0$ Hz, 1 H), 1.27 (d, $J=7.0$ Hz, 6 H);
CIMS (isobutane) m/e 313 (MH^+ , 100). Anal. ($C_{20}H_{24}O_3$) C,
H.

5 (Z)-1-(4-*t*-Butylphenyl)-2-(3,4,5-trimethoxy-
phenyl)ethene (15g): 192 mg; 31%; oil; 1H NMR ($CDCl_3$,
200 MHz) δ 7.29 (d, $J=8.4$ Hz, 2 H), 7.23 (d, $J=8.4$ Hz, 2
H), 6.60 (d, $J=12.2$ Hz, 1 H), 6.46 (d, $J=12.2$ Hz, 1 H),
6.45 (s, 2 H), 3.83 (s, 3 H), 3.64 (s, 6 H), 1.29 (s, 9
H); CIMS (isobutane) m/e 327 (MH^+ , 100%). Anal.
10 ($C_{21}H_{26}O_3$) C, H.

(Z)-1-(4-Methoxyphenyl)-2-(3,4-dimethoxy-
phenyl)ethene (15h): 280 mg; 46%; oil; 1H NMR ($CDCl_3$,
200 MHz) δ 7.23 (d, $J=8.8$ Hz, 2 H), 6.83-6.75 (m, 5 H),
6.46 (s, 2 H), 3.87 (s, 3 H), 3.79 (s, 3 H), 3.65 (s, 3
H); CIMS (isobutane) m/e 271 (MH^+ , 100). Anal. ($C_{17}H_{18}O_3$)
15 C, H.

(Z)-1-(3,5-Dimethoxyphenyl)-2-(4-methoxy-
phenyl)ethene (15i): 241 mg; 45%; oil; 1H NMR ($CDCl_3$,
200 MHz) δ 7.22 (d, $J=8.8$ Hz, 2 H), 6.77 (d, $J=8.8$ Hz, 2
H), 6.54 (d, $J=12.2$ Hz, 1 H), 6.46 (d, $J=2.3$ Hz, 2 H),
20 6.44 (d, $J=12.2$ Hz, 1 H), 6.32 (t, $J=2.3$ Hz, 1 H), 3.79
(s, 3 H), 3.67 (s, 6 H); CIMS (isobutane) m/e 271 (MH^+ ,
100). Anal. ($C_{17}H_{18}O_3$) C, H.

(Z)-1-[4-(Benzyloxy)-3,5-(dimethoxy)phenyl]-2-
25 (4-methoxyphenyl)ethene (15j): 294 mg; 33%; oil; 1H NMR
($CDCl_3$, 200 MHz) δ 7.52-7.45 (m, 2 H), 7.41-7.26 (m, 3
H), 7.21 (d, $J=8.7$ Hz, 2 H), 6.78 (d, $J=8.75$ Hz, 2 H),
6.52 (d, $J=12.1$ Hz, 1 H), 6.49 (s, 2 H), 6.42 (d, $J=12.1$
Hz, 1 H), 5.01 (s, 2 H), 3.79 (s, 3 H), 3.66 (s, 6 H);
CIMS (isobutane) m/e 377 (MH^+ , 100). Anal. ($C_{24}H_{24}O_4$) C,
30 H.

1 (Z)-1-[4-((t-Butyldimethylsilyl)-oxy)-3,5-
(dimethoxy)-phenyl]-2-(4-methoxyphenyl)ethene (15k):
277 mg; 35%; oil; ^1H NMR (CDCl_3 , 200 MHz) δ 7.23 (d, $J=8.8$
5 Hz, 2 H) 6.76 (d, $J=8.8$ Hz, 2 H), 6.49 (s, 2 H), 6.45
(s, 2 H), 3.78 (s, 3 H), 3.63 (s, 6 H), 1.02 (s,
9 H), 0.14 (s, 6 H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 159.21
151.90, 134.04, 129.63, 129.21, 113.95, 106.47, 55.86,
55.51, 26.06, 18.96, -4.49. Anal. ($\text{C}_{23}\text{H}_{22}\text{O}_4\text{Si}$) C, H.

10 (E)-1-(4-n-Propoxyphenyl)-2-(3,4,5-tri-
methoxyphenyl)ethene (16b): 187 mg; 28%; mp 82-83°C; ^1H
NMR (CDCl_3 , 200 MHz); δ 7.44 (d, $J=8.8$ Hz, 2 H), 6.95-
6.87 (m, 4 H), 6.72 (s, 2 H), 3.93 (t, $J=6.6$ Hz, 2 H),
3.91 (s, 6 H), 3.89 (s, 3 H), 1.82 (sextet, $J=6.6$ Hz, 2
H), 1.04 (t, $J=6.6$ Hz, 3 H); CIMS (isobutane) m/e 329
15 MH^+ , 100). Anal. ($\text{C}_{20}\text{H}_{24}\text{O}_4$) C, H.

20 (E)-(4-Methylphenyl)-2-(3,4,5-
trimethoxyphenyl)ethene (16d): 121 mg; 21%; mp 125-
127°C; ^1H NMR (CDCl_3 , 200 MHz) δ 7.40 (d, $J=8.1$ Hz, 2 H),
7.16 (d, $J=8.1$ Hz, 2 H), 6.98 (s, 2 H), 6.73 (s, 2 H),
3.91 (s, 6 H), 3.87 (s, 3 H), 2.35 (s, 3 H); ^{13}C NMR
(CDCl_3 , 200 MHz) δ 153.84, 138.19, 137.90, 134.81,
133.68, 129.80, 128.50, 128.00, 126.71, 103.74, 61.12,
56.25, 21.30; CIMS (isobutane) m/e 285 (MH^+ , 100).
Anal. ($\text{C}_{18}\text{H}_{20}\text{O}_3$) C, H.

25 (E)-(4-Ethylphenyl)-2-(3,4,5-
trimethoxyphenyl)ethene (16e): 182 mg; 30%; mp 98-
100°C; ^1H NMR (CDCl_3 , 200 MHz) δ 7.44 (d, $J=8.1$ Hz, 2 H),
7.20 (d, $J=8.1$ Hz, 2 H), 7.00 (s, 2 H), 6.74 (s, 2 H),
3.92 (s, 6 H), 3.87 (s, 3 H), 2.66q, $J=7.4$ Hz, 2 H),
1.26 (t, $J=7.4$ Hz, 3 H); CIMS (isobutane) m/e 299 (MH^+ ,
30 100). Anal. ($\text{C}_{19}\text{H}_{22}\text{O}_3$) C, H.

1 (E)-[4-(2-Propyl)phenyl]-2-(3,4,5-
trimethoxyphenyl)ethene (16f): 151 mg; 24%; mp 74-75°C;
5 ¹H NMR (CDCl₃, 200 MHz) δ 7.45 (d, J=8.2 Hz, 2 H), 7.23
(d, J=8.2 Hz, 2 H), 7.00 (s, 2 H), 6.74 (s, 2 H), 3.93
(s, 6 H), 3.87 (s, 3 H), 2.92 (sextet, J=7.0 Hz, 1 H),
1.27 (d, J=7.0 Hz, 6 H); CIMS (isobutane) m/e 313 (MH⁺,
100). Anal. (C₂₀H₂₄O₃) C, H.

(E)-1-(4-t-Butylphenyl)-2-(3,4,5-
trimethoxyphenyl)ethene (16g): 143 mg; 23%; mp 127-
10 128°C; ¹H NMR (CDCl₃, 200 MHz) δ 7.46 (d, J=8.7 Hz, 2 H),
7.38 (d, J=8.7 Hz, 2 H), 7.0 (s, 2 H), 6.74 (s, 2 H),
3.92 (s, 6 H), 3.87 (s, 3 H), 1.34 (s, 9 H); CIMS
(isobutane) m/e 327 (MH⁺, 100%). Anal. (C₂₁H₂₆O₃) C, H.

(E)-(4-Methoxyphenyl)-2-(3,4-
15 dimethoxyphenyl)ethene (16h): 110 mg; 20%; mp 135-
137°C.

(E)-1-(3,5-Dimethoxyphenyl)-2-(4-
methoxyphenyl)ethene (16i): 123 mg; 23%; mp 55-56°C.

(E)-1-[4-(Benzyloxy)-3,5-(dimethoxy)phenyl]-2-
20 (4-methoxyphenyl)ethene (16j): 207 mg; 28%; mp 104-
105°C; ¹H NMR (CDCl₃, 200 MHz) δ 7.55-7.48 (m, 2 H), 7.45
(d, J=8.8 Hz, 2 H), 7.40-7.25 (m, 3 H), 6.98 (d, J=16.1
Hz, 1 H), 6.90 (d, J=8.8 Hz, 2 H), 6.89 (d, J=16.1 Hz, 1
H), 6.71 (s, 2 H), 5.03 (s, 2 H), 3.87 (s, 6 H), 3.83
(s, 3 H); CIMS (isobutane) m/e 377 (MH⁺, 100). Anal.
25 (C₂₄H₂₄O₄) C, H.

(E)-1-[4-[(t-Butyldimethylsilyl)-oxy]-3,5-
(dimethoxy)-phenyl]-2-(4-methoxyphenyl)ethene (16k):
224 mg; 28%; mp 118-120°C; ¹H NMR (CDCl₃, 200 MHz) δ 7.42
(d, J=8.8 Hz, 2 H), 6.91 (s, 2 H), 6.88 (d, J=8.8 Hz, 2
30 H), 6.69 (s, 2 H), 3.84 (s, 6 H), 3.82 (s, 3 H), 1.01
(s, 9 H), 0.14 (s, 6 H); ¹³C NMR (CDCl₃, 50 MHz) δ 159.67,

1 152.33, 130.97, 130.87, 127.98, 127.49, 127.04, 114.59,
103.93, 56.08, 55.61, 26.03, 18.54, -4.42. Anal.
(C₂₃H₃₂O₄Si) C, H.

Preparation of acetates 15i and 16i. A
5 solution of n-Bu₄NF in THF (1 M, 2 mL, 2 mmol) was added
to a solution of stilbenes 15k and 16k (400 mg, 1 mmol)
in THF (5 mL) and the mixture was stirred at 0°C. After
30 min., acetic anhydride (0.5 mL) was added, and
stirring was continued at room temperature for 24 h.
10 Solvents were evaporated at reduced pressure and the
residue was mixed with water (50 mL). The product was
extracted with ether (2 x 25 mL) and the ether solution
was washed with water (2 x 100 mL). Evaporation of the
solvents and purification of the crude product by
15 preparative TLC using 40% EtOAc in hexane as the eluent
afforded the desired products.

(Z)-1-(4-Acetoxy-3,5-dimethoxyphenyl)-2-(4-
methoxyphenyl)ethene (15i): 111 mg; 33%; oil; ¹H NMR
(CDCl₃, 200 MHz) δ 7.24 (d, J=8.6 Hz, 2 H), 6.78 (d,
J=8.6 Hz, 2 H), 6.55 (d, J=12.1 Hz, 1 H), 6.53 (s, 2 H),
20 6.43 (d, J=12.1 Hz, 1 H), 3.77 (s, 3 H), 3.64 (s, 6 H),
2.32 (s, 3 H); ¹³C NMR (CDCl₃, 50 MHz) δ 169.27, 159.27,
152.24, 136.00, 130.66, 130.53, 129.79, 128.84, 127.93,
113.91, 105.85, 56.11, 55.37, 20.51; CIMS (isobutane)
m/e 329 (MH⁺, 100). Anal. (C₁₉H₂₀O₅) C, H.

25 (E)-1-(4-Acetoxy-3,5-dimethoxyphenyl)-2-(4-
methoxy-phenyl)ethene (16i): 137 mg; 41%; mp 129-131°C;
¹H NMR (CDCl₃, 200 MHz) δ 7.45 (d, J=8.8 Hz, 2 H), 6.97-
6.88 (m, 4 H), 6.73 (s, 2 H), 3.87 (s, 6 H), 3.83 (s, 3
H), 2.35 (s, 3 H); ¹³C NMR (CDCl₃, 50 MHz) δ 169.35,
30 159.87, 152.70, 136.55, 130.18, 128.95, 128.13, 126.73,

1 114.48, 103.16 56.28, 55.48, 20.55; CIMS (isobutane) m/e
329 (MH⁺, 100). Anal. (C₁₉H₂₀O₅) C, H.

General procedure for the preparation of
dihydrostilbenes 17a-e. A mixture of E-stilbenes (16)
5 and the corresponding Z-stilbenes (15) (1 mmol) in EtOAc
was hydrogenated at 40 psi in the presence of 10%
palladium on charcoal (50 mg) for 4 h. The catalyst was
removed by filtration, and the filtrate was
concentrated, yielding the dihydrostilbene derivatives
17a-c. Analytical samples were prepared by preparative
10 thin-layer chromatography on silica gel using 20% EtOAc
in hexane as the eluent.

1-(4-Ethoxyphenyl)-2-(3,4,5-
trimethoxyphenyl)ethane (17a): 250 mg; 80%; oil; ¹H NMR
(CDCl₃, 200 MHz) δ7.06 (d, J=8.5 Hz, 2 H), 6.80 (d,
15 J=8.5 Hz, 2 H), 6.34 (s, 2 H), 4.32 (q, J=7.3 Hz, 2 H),
3.81 (s, 3 H), 3.80 (s, 6 H), 2.82 (s, 4 H), 1.40 (t,
J=7.3 Hz, 3 H); CIMS (isobutane) m/e 317 (MH⁺, 100%).
Anal. (C₁₉H₂₄O₄) C, H.

1-(4-n-Propoxyphenyl)-2-(3,4,5-
20 trimethoxyphenyl)ethane (17b): 284 mg; 86%; oil; ¹H NMR
(CDCl₃, 200 MHz) δ7.09 (d, J=8.6 Hz, 2 H), 6.83 (d,
J=8.6 Hz, 2 H), 6.37 (s, 2 H), 3.90 (t, J=6.6 Hz, 2 H),
3.82 (s, 9 H), 2.84 (s, 4 H), 1.80 (m, 2 H), 1.03 (t,
J=7.4 Hz, 3 H); CIMS (isobutane) m/e 331 (MH⁺, 100).
25 Anal. (C₂₀H₂₆O₄) C, H.

1-(4-Methylthiophenyl)-2-(3,4,5-
trimethoxyphenyl)ethane (17c): 276 mg; 86%; mp 52-54°C;
¹H NMR (CDCl₃, 200 MHz) δ7.21 (d, J=8.1 Hz, 2 H), 7.11
(d, J=8.1 Hz, 2 H), 6.36 (s, 2 H), 3.82 (bs, 9 H), 2.86
30 (bs, 4 H), 2.47 (s, 3 H); CIMS (isobutane) m/e 319 (MH⁺,
100). Anal. (C₁₈H₂₂O₃S) C, H.

1- (4-Methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethane (17d): 247 mg; 86%; mp 51-52°C; ¹H NMR (CDCl₃, 200 MHz) δ 7.09 (s, 4 H), 6.38 (s, 2 H), 3.83 (s, 3 H), 3.82 (s, 6 H), 2.85 (bs, 4 H), 2.32 (s, 3 H); CIMS (isobutane) m/e 287 (MH⁺, 100). Anal. (C₁₈H₂₂O₃) C, H.

1- (4-Ethylphenyl)-2-(3,4,5-trimethoxyphenyl)ethane (17e): 261 mg; 87%; oil: ¹H NMR (CDCl₃, 200 MHz) δ 7.12 (s, 4 H), 6.37 (s, 2 H), 3.83 (s, 3 H), 3.82 (s, 6 H), 2.86 (bs, 4 H), 2.63 (q J=7.6 Hz, 2 H), 1.23 (t, J=7.6 Hz, 3 H); CIMS (isobutane) m/e 299 (MH⁺, 100). Anal. (C₁₉H₂₂O₃) C, H.

General procedure for the preparation of Compounds 17f-g. A mixture of 1-(4-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethane (18) 288 mg, 1 mmol), aminoalkyl chloride hydrochloride 19a-b (1.1 mmol) and potassium carbonate (276 mg, 2 mmol) in acetone (15 mL) was heated at reflux for 12 h, and the solids were removed by filtration. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel using 5% methanol in CHCl₃ as the eluent. All these compounds were obtained as viscous oils.

1-[4-(2-N,N-Dimethylaminoethoxy)phenyl]-2-(3,4,5-trimethoxyphenyl)ethane (17f): 243 mg; 68%; oil; ¹H NMR (CDCl₃, 500 MHz) δ 7.08 (d, J=8.5 Hz, 2 H), 6.85 (d, J=8.5 Hz, 2 H), 6.36 (s, 2 H), 4.09 (t, J=5.5 Hz, 2 H), 3.82 (s, 3 H), 3.81 (s, 6 H), 2.85-2.80 (m, 6 H), 2.41 (s, 6 H); CIMS (isobutane) m/e 360 (MH⁺, 100). Anal. (C₂₁H₂₉O₄) C, H.

1-[4-(2-N,N-Diethylaminoethoxy)phenyl]-2-(3,4,5-trimethoxyphenyl)ethane (17g): 296 mg; 76%; oil; ¹H NMR (CDCl₃, 500 MHz) δ 7.10 (d, J=8.5 Hz, 2 H), 6.84

1 (d, J=8.5 Hz, 2 H), 6.38 (s, 2 H), 4.08 (t, J=6.2 Hz, 2 H), 3.85 (s, 3 H), 3.84 (s, 6 H), 2.94 (t, J=6.2 Hz, 2 H), 2.86-2.82 (m, 4 H), 2.71 (q, J=7.1 Hz, 4 H), 1.11 (t, J=7.1 Hz, 6 H); CIMS (isobutane) m/e 388 (MH⁺, 100).
5 Anal. (C₂₃H₃₃NO₄) C, H.

Typical procedure for preparation of compounds 17h-j. A solution of compound 20a (2 mmol) in THF (20 mL) was added to a well-stirred solution of LDA (2 mmol) in THF (22 mL) at -78°C, and stirring continued for 30 min. To this 4-methoxybenzyl bromide (21a) (2 mmol) was
10 added, and stirring continued at -78°C for 1 h and at room temperature for 6 h. The reaction mixture was quenched by the addition of glacial acetic acid (2 mL) and the solvents were distilled off at reduced pressure. The residue was treated with water (20 mL) and the
15 solvents were distilled off at reduced pressure. The residue was treated with water (20 mL) and the product was extracted with ether (2 x 70 mL). The combined ether extracts were washed with water and dried (Na₂SO₄). Evaporation of the ether and re-crystallization of the
20 residue from CH₂Cl₂-hexane gave compound 17h. Compounds 17i and 17j were prepared by using the same method.

3-(4-Methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)propanonitrile (17h): 320 mg; 49%; mp 82-83°C; ¹H NMR (CDCl₃, 200 MHz) δ 7.05 (d, J=8.5 Hz, 2
25 H), 6.83 (d, J=8.5 Hz, 2 H), 6.41 (s, 2 H), 3.89 (t, J=7.2 Hz, 1 H), 3.84 (s, 3 H), 3.81 (s, 6 H), 3.78 (s, 3 H), 3.12-3.07 (m, 2 H); CIMS (isobutane) m/e 328 (MH⁺, 100). Anal. (C₁₉H₂₁NO₄) C, H.

2-(4-Methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)propanonitrile (17i): 450 mg; 69%; mp 102-103°C; ¹H NMR (CDCl₃, 200 MHz) δ 7.13 (d, J=8.5 Hz,
30

1 2 H), 6.85 (d, J=8.5 Hz, 2 H), 6.28 (s, 2 H), 3.92 (t, J=6.7 Hz, 1 H), 3.80 (s, 3 H), 3.76 (s, 3 H), 3.75 (s, 6 H), 3.06-3.00 (m, 2 H); CIMS (isobutane) m/e 328 (MH⁺, 100). Anal. (C₁₉H₂₁NO₄) C, H.

5 Methyl 2-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)n-proponate (17j): 533 mg; 74%; mp 84-5°C; ¹H NMR (CDCl₃, 200 MHz) δ 7.22 (d, J=8.5 Hz, 2 H), 6.85 (d, J=8.5 Hz, 2 H), 6.29 (s, 2 H), 3.80 (s, 3 H), 3.78 (s, 6 H), 3.77 (s, 3 H), 3.62 (s, 3 H), 3.42-3.24 (m, 2 H), 3.00 (m, 1 H); CIMS (isobutane) m/e 361 (MH⁺, 100%). Anal. (C₂₀H₂₄O₆) C, H.

10 General procedure for the preparation of Compounds 23a-c. A mixture of phenylacetic acid 22a-b (2 mmol), benzaldehyde 131-m (2 mmol) and triethylamine (0.5 mL) in acetic anhydride (5 mL) was heated at reflux for 12 h and poured into hot saturated sodium carbonate solution (50 mL) and left overnight. The mixture was extracted with ether (2 x 50 mL), and the ether extracts were discarded. The aqueous solution was acidified with dil. HCl and the precipitated product was filtered and dried. Recrystallization from EtOAc-hexane gave pure product.

25 (E)-3-(4-Methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-enoic acid (23a): 523 mg; 76%; mp 187-189°C; ¹H NMR (CDCl₃, 200 MHz) δ 9.8 (bs, 1 H), 7.89 (s, 1 H), 7.07 (d, J=8.9 Hz, 2 H), 6.73 (d, J=8.9 Hz, 2 H), 6.47 (s, 2 H), 3.91 (s, 3 H), 3.79 (s, 6 H), 3.78 (s, 3 H); ¹³C NMR (CDCl₃, 50 MHz) δ 173.90, 161.31, 154.15, 142.79, 138.04, 133.26, 131.51, 129.09, 127.07, 114.19, 106.87, 61.14, 56.25, 55.43; CIMS (isobutane) m/e 345 (MH⁺, 100). Anal. (C₁₉H₂₀O₆) C, H.

1 (E)-3-(3-Methoxyphenyl)-2-(3,4,5-
trimethoxyphenyl)-prop-2-enoic acid (23b): 483 mg; 70%;
mp 178-180°C; ¹H NMR (CDCl₃, 200 MHz) δ 8.70 (bs, 1 H),
7.90 (s, 1 H), 7.15 (t, J=8.1 Hz, 1 H), 6.85-6.76 (m, 2
5 H), 6.62 (bs, 1 H), 6.49 (s, 2 H), 3.88 (s, 3 H), 3.78
(s, 6 H), 3.55 (s, 3 H); CIMS (isobutane) m/e 345 (MH⁺,
100). Anal. (C₁₉H₂₀O₆) C, H.

(E)-2-(4-Methoxyphenyl)-3-(3,4,5-
trimethoxyphenyl)-prop-2-enoic acid (23c): 468 mg; 68%;
10 mp 206-207°C.

Preparation of compounds 24a-b. Conc. H₂SO₄
(0.5 mL) was added to a stirred solution of carboxylic
acid 23a-b (172 mg, 0.5 mmol) in absolute methanol (20
mL), and the mixture was heated under reflux for 6 h.
15 About 90% of the excess methanol was removed by
evaporation, and the residue was poured into ice-water
(300 mL). The product was extracted with ether (2 x 40
mL), and the combined extracts were washed with 2%
aqueous NaOH solution (2 x 50 mL) followed by water (200
20 mL). Evaporation of the ether from the dried (Na₂SO₄)
solution gave the desired products.

(E)-Methyl 3-(4-methoxyphenyl)-2-(3,4,5-
trimethoxyphenyl)-prop-2-enoate (24a): 316 mg; 88%; mp
74-75°C; ¹H NMR (CDCl₃, 200 MHz) δ 7.77 (s, 1 H), 7.03 (d,
J=9.0 Hz, 2 H), 6.72 (d, J=9.0 Hz, 2 H), 6.44 (s, 2 H),
25 3.91 (s, 3 H), 3.81 (s, 3 H), 3.78 (s, 6 H), 3.77 (s, 3
H); CIMS (isobutane)m/e 359 (MH⁺, 100). Anal. (C₂₀H₂₂O₆)
C, H.

(E)-Methyl 3-(3-methoxyphenyl)-2-(3,4,5-
trimethoxy-phenyl)-prop-2-enoate (24b): 308 mg; 86%; mp
30 87-88°C; ¹H NMR (CDCl₃, 200 MHz) δ 7.79 (s, 1 H), 7.13 (t,
J=8.1 Hz, 1 H), 6.82-6.70 (m, 2 H), 6.59 (bs, 1 H), 6.46

1 (s, 2 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.77 (s, 6 H),
3.54 (s, 3 H); CIMS (isobutane) m/e 359 (MH^+ , 100).

Anal. ($C_{20}H_{22}O_6$) C, H.

(E)-N-Methyl-[3-(4-methoxyphenyl)-2-(3,4,5-
5 trimethoxyphenyl)]-prop-2-enoamide (24c). A mixture of
carboxylic acid 23a (172 mg, 0.5 mmol) and thionyl
chloride (1 mL) in benzene (10 mL) was refluxed for 6 h.
The excess thionyl chloride and benzene were removed at
reduced pressure and the residue was kept under vacuum
for 30 min. It was subsequently mixed with aqueous
10 methylamine solution (40%, 5 mL) and kept at room
temperature for 2 h. The precipitated product was
filtered, washed sequentially with 2% NaOH solution and
water, and dried. An analytical sample was prepared by
recrystallization from EtOAc-hexane. 156 mg; 87%; mp
15 172-174°C; 1H NMR ($CDCl_3$, 200 MHz) δ 7.79 (s, 1 H), 6.99
(d, J=8.8 Hz, 2 H), 6.71 (d, J=8.8 Hz, 2 H), 6.46 (s,
2 H), 5.10 (bq, 1 H), 3.94 (s, 3 H), 3.81 (s, 6 H), 3.76
(s, 3 H), 2.87 (d, J=4.8 Hz, 3 H); CIMS (isobutane) m/e
358 (MH^+ , 100). Anal. ($C_{20}H_{23}O_5$) C, H.

20 Preparation of compounds 24d-f. A solution of
ethylamine (0.5 mL) or the appropriate amino alcohol
(0.5 mmol) in THF (5 mL) was added to a solution of the
acid chlorides (prepared from 23a-b in 0.5 mmol scale,
as described above) in THF (10 mL). The mixture was
25 stirred for 3 h. Solvents were removed at reduced
pressure, and the residue was poured onto ice (200 g).
The product was extracted with ether (2 x 20 mL), washed
with water, and dried (Na_2SO_4). Evaporation of ether
gave crude products. Product 24d was purified by
30 recrystallization from EtOAc-hexane and the liquid

1 products 24e and 24f were purified by column
chromatography on silica gel using ether as the eluent.

(E)-N-Ethyl-[3-(4-methoxyphenyl)-2-(3,4,5-
trimethoxyphenyl)]-prop-2-enoamide (24d): 149 mg; 80%;
mp 152-154°C; ¹H NMR (CDCl₃, 200 MHz) δ 7.77 (s, 1 H),
5 6.99 (d, J=8.4 Hz, 2 H), 6.70 (d, J=8.4 Hz, 2 H), 6.46
(s, 2 H), 5.58 (bt, 1 H), 3.95 (s, 3 H), 3.80 (s, 6 H),
3.76 (s, 3 H), 3.36 (q, J=7.1 Hz, 2 H), 1.11 (t, J=7.1
Hz, 3 H); CIMS (isobutane) m/e 372 (MH⁺, 100). Anal.
10 (C₂₁H₂₅NO₅) C, H.

(E)-(2-N,N-Diethylamino)ethyl-3-(4-methoxy-
phenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-enoate (24e):
192 mg; 87%; oil; ¹H NMR (CDCl₃, 200 MHz) δ 7.77 (s, 1 H),
7.06 (d, J=8.8 Hz, 2 H), 6.72 (d, J=8.8 Hz, 2 H), 6.44
(s, 2 H), 4.28 (t, J=6.1 Hz, 2 H), 3.90 (s, 3 H), 3.78
15 (s, 6 H), 3.77 (s, 3 H), 2.77 (t, J=6.1 Hz, 2H), 2.55
(q, J=7.2 Hz, 4 H), 1.01 (t, J=7.2 Hz, 6H); ¹³C NMR
(CDCl₃, 50 Mhz) δ 168.49, 160.90, 154.06, 140.53, 137.88,
132.88, 132.16, 130.19, 127.42, 114.10, 106.89, 63.94,
61.14, 56.25, 55.41, 50.98, 47.89, 12.04; CIMS
20 (isobutane) m/e 444 (MH⁺, 100). Anal. (C₂₅H₃₃NO₆) C, H.

(E)-(2-N,N-Diethylamino)ethyl-3-(3-methoxy-
phenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-enoate (24f):
201 mg; 91%; oil; ¹H NMR (CDCl₃, 200 MHz) δ 7.78 (s, 1 H),
7.13 (d, J=7.9 Hz, 1 H), 6.80-6.74 (m, 2 H), 6.61-6.59
25 (m, 1 H), 6.46 (s, 2 H), 4.30 (t, J=6.1 Hz, 2 H), 3.87
(s, 3 H), 3.78 (s, 6 H), 3.54 (s, 3 H), 2.77 (t, J=6.1
Hz, 2 H), 2.56 (q, J=7.1 Hz, 4 H), 1.05 (t, J=7.1 Hz, 6
H); CIMS (isobutane) m/e 444 (MH⁺, 100). Anal.
(C₂₅H₃₃NO₆) C, H.

30 3,4,4',5-Tetramethoxybenzophenone (27).

Anhydrous AlCl₃ (260 mg, 2 mmol) was added to a well-

1 stirred solution of 3,4,5-trimethoxybenzoyl chloride
(25) (461 mg, 2 mmol) and anisole (216 mg, 2 mmol) at
0°C in CH_2Cl_2 (25 mL). The mixture was stirred while
allowing it to warm to room temperature. After 6 h, the
5 resultant dark reaction mixture was poured into ice cold
5% HCl (20 mL), and the CH_2Cl_2 layer was separated. The
aqueous layer was extracted with an additional 30 mL of
 CH_2Cl_2 , and the combined CH_2Cl_2 solutions were washed
with saturated sodium bicarbonate solution. Evaporation
10 of solvents from the dried CH_2Cl_2 extract and
purification of the residue by chromatography on a
column of silica gel, using 5% EtOAc in hexane as
eluent, gave product 27 (487 mg, 80%); mp 72-73°C; ^1H
NMR (CDCl_3 , 200 MHz) δ 7.83 (d, J=8.7 Hz, 2 H), 7.03 (s,
2 H), 6.98 (d, J=8.7 Hz, 2 H), 3.94 (s, 3 H), 3.90 (s, 3
15 H), 3.88 (s, 6 H); CIMS (isobutane) m/e 303 (MH^+ , 100).
Anal. ($\text{C}_{17}\text{H}_{18}\text{O}_5$), C, H.

4-Methoxyphenyl-(3,4,5-trimethoxyphenyl)-
methanol (28). Sodium borohydride (76 mg, 2 mmol) was
added in small portions to a well-stirred solution of
20 3,4,4',5-tetramethoxybenzophenone (27) (302 mg, 1 mmol)
in ethanol (15 mL) at 0°C in 15 min and the resultant
mixture was stirred for 3 h at room temperature. The
reaction was quenched by careful addition of glacial
acetic acid (1 mL), and the solvents were removed at
25 reduced pressure. The residue was poured into water,
and the product was extracted with ether (2 x 50 mL).
The combined ether extracts were washed with saturated
 NaHCO_3 solution, followed by water, and dried (Na_2SO_4).
Evaporation of solvents and crystallization of the
30 residue from EtOAc-hexane gave product 28 as a white
crystalline solid (287 mg, 94%); mp 104-105°C; ^1H NMR

1 (CDCl₃, 200 MHz) δ 7.29 (d, J=8.7 Hz, 2 H), 6.88 (d, J=8.7 Hz, 2 H), 6.60 (s, 2 H), 5.73 (d, J=3.2 Hz, 1 H), 3.82 (s, 9 H), 3.80 (s, 3 H), 2.32 (d, J=3.2 Hz, 1 H); CIMS (isobutane) m/e 305 (MH⁺, 100). Anal. (C₁₇H₂₀O₅) C, H.

5 4-Methoxyphenyl-(3,4,5-trimethoxyphenyl)-methane (29). A solution of 28 (304 mg, 1 mmol) in EtOAc (20 mL) was hydrogenated at 60 psi in the presence of 10% Pd-C (60 mg) for 12 h. The solution was
10 filtered, and solvents were evaporated. The crude product was purified by crystallization from EtOAc and hexane (183 mg, 60%); mp 66-67°C; ¹H NMR (CDCl₃, 200 MHz) δ 7.12 (d, J=8.5 Hz, 2 H), 6.85 (d, J=8.5 Hz, 2 H), 6.39 (s, 2 H), 3.87 (s, 2 H), 3.82 (s, 3 H), 3.81 (s, 6 H), 3.79 (s, 3 H); CIMS (isobutane) m/e 289 (MH⁺, 100).
15 Anal. (C₁₇H₂₀O₄) C, H.

2,3,4,7-Tetramethoxyphenanthrene (32). A mixture of 30a and 31a (1.1g 3.6 mmol) was dissolved in cyclohexane (500 ml) containing iodine (60 mg) and acetophenone (0.22 ml, 0.5 eq). The solution was
20 irradiated with a 450 W medium pressure mercury UV lamp for 6 h with stirring and cooling. TLC showed that the starting material had disappeared. The solvent was evaporated and the residue subjected to flash
25 chromatography (ether:hexane, 30:70 by volume, silica gel 230-400 mesh) to give 32a (460 mg) and 32c (560 mg, 92.7% total yield): 32a, pale yellow oil; IR (KBr) 836 (2H adjacent), 760 cm⁻¹ (3 H adjacent); ¹H NMR (CDCl₃, 500 MHz) δ 7.30-7.50 (m, 3 H), 7.00-7.10 (m, 3 H), 4.00 (s, br, 9 H), 3.70 (s, 3 H). EIMS m/e 298 (M⁺, 58), 283
30 (11); Anal. (C₁₈H₁₈O₄) C, H.

1 2,3,4,7-Tetramethoxyphenanthrene (32c). This
compound was obtained as white crystals from ethyl
acetate and hexane as described above: mp 142-144°C; IR
(KBr) 866 (1H), 831 cm^{-1} (2 H adjacent); ^1H NMR (CDCl_3 ,
500 MHz) 59.41 (d, 1 H), 7.60 (s, 2 H), 7.23-7.21 (m, 2
5 H), 7.08 (s, 1H). 4.03 (s, 3 H), 4.01 (s, 3 H), 4.00 (s,
3 H), 3.96 (s, 3 H); EIMS m/e 298 (M^+ , 100), 283 (41).
Anal. ($\text{C}_{18}\text{H}_{18}\text{O}_4$): C, H.

 2,3,4,6-Tetramethoxyphenanthrene (32b).
10 Compound 23b (460 mg, 58% yield) was prepared by
irradiation of a mixture of 30b and 31b (800 mg, 2.66
mmol) in hexane (500 mL) as described above: mp 68-
70°C; IR (KBr) 865 (1 H), 843 cm^{-1} (2 H adjacent); ^1H NMR
(CDCl_3 , 200 MHz) 59.06 (d, 1 H, $J=4$ Hz), 7.75 (d, 1 H,
15 $J=8$ Hz), 7.60 (d, 1 H, $J=8.6$ and 8.8 Hz), 7.47 (d, 1 H,
 $J=8$ Hz), 7.22 (dd 1H $J=8.6$ and 2.8 Hz), 7.08 (s, 1 H),
4.02 (s, 6 H), 4.01 (s, 3 H), 4.00 (s, 3 H). EIMS m/e
298 (M^+ , 100), 283 (45). Anal. ($\text{C}_{18}\text{H}_{18}\text{O}_4$), C, H.

 2,3,4,8-Tetramethoxyphenanthrene (32d). The
stilbene mixture containing 30c and 31c (1010 mg, 3.36
20 mmol) in cyclohexane (500 mL) containing iodine (53 mg)
and acetophenone (1.71 mmol, 0.5 eq) was irradiated as
in the above synthesis of 32a and 32c to give 32d (760
mg, 76%): mp 80-82°C; IR (KBr) 846 (2 H adjacent), 790
 cm^{-1} (3 H adjacent); ^1H NMR (CDCl_3 , 200 Mhz) 59.12 (d, 1
25 H, $J=10$ Hz), 8.20 (d, 1 H, $J=10$ Hz), 7.57 (m, 2 H), 7.10
(s, 1 H), 6.99 (d, 1 H, $J=8$ Hz), 4.03 (s, 6 H), 4.02 (s,
3 H), 4.00 (s, 3 H); EIMS m/e 298 (M^+ , 100), 283 (40).
Anal. ($\text{C}_{18}\text{H}_{18}\text{O}_4$) C, H.

 2-(4-Methoxyphenyl)-3-(3,4,5-
30 trimethoxyphenyl)propionic acid (33). A mixture of the
ester 17j (3.0 g, 8.3 mmol) in ethanol (50 mL) and

1 potassium hydroxide (4.0 g, 71 mmol) in ethanol:water
(60 mL, 4:1 by volume) was heated at reflux under Ar
until most of the starting material disappeared (about
24 h). The reaction solution was poured into ice-cold
5 water (500 mL) and acidified with 20% sulfuric acid (200
mL), extracted with ether (100, 100, 50 mL), washed with
water (50 mL) and saturated sodium chloride solution (50
mL), and dried over anhydrous sodium sulfate.

Evaporation of the filtrate and flash chromatography
(ether: hexane, 70:30 by volume, silica gel 230-400
10 mesh) gave 33 as a yellow oil (1.97 g, 79.1%): IR
(film) 3231 (br), 3005, 2933, 1733, 1703, 1590, 1513,
1462, 1421, 1246, 1180, 1123 cm^{-1} ; ^1H NMR (CDCl_3 , 200
MHz) δ 7.32 (d, 2 H, $J=10$ Hz), 6.85 (d, 2 H, $J=10$ Hz),
15 6.83 (s, 2 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.77 (m, 1
H), 3.74 (s, 6 H), 3.31 (m, 1 H), 2.95 (m, 1 H). FABMS
m/e 347 (MH^+ , 39.2).

2-(4-Methoxyphenyl)-4,5,6-trimethoxyindan-3-
one (34). A solution of the acid 33 (0.5 g, 1.4 mmol)
20 in phosphorous oxychloride (5 mL, 53.4 mmol) was heated
at reflux for 3 min. The dark red solution was poured
onto crushed ice (about 30 g) and extracted with ether
(50, 20, and 20 mL). The combined ether layer was dried
over anhydrous sodium sulfate. Evaporation of the
filtrate gave a gray solid. Recrystallization of this
25 gray solid from ethyl acetate and hexane afforded pale
gray crystals 0.32 g (69.6%): mp 104-106°C; IR (KBr)
3010, 2960, 1697, 1595, 1512, 1323, 1251, 1139 cm^{-1} ; ^1H
NMR (CDCl_3 , 200 MHz) δ 7.11 (d, 2 H, $J=8$ Hz), 6.85 (d, 2
H, $J=8$ Hz), 6.71 (s, 1 H), 4.03 (s, 3 H), 3.96 (s, 3 H),
30 3.87 (s, 3 H), 3.78 (s, 3 H), 3.78 (m, 1 H), 3.54 (m, 1

1 H), 3.10 (m, 1 H); EIMS m/e 328 (M^+ , 98). Anal.
($C_{19}H_{20}O_5$), C, H.

2-(4-Methoxyphenyl)-4,5,6-trimethoxyindane
(35). A mixture of the ketone 34 (250 mg, 0.74 mmol)
and 10% Pd-C (100 mg) in acetic acid (40 mL) was
5 subjected to hydrogenolysis at 42 psi hydrogen pressure
until the absorption of hydrogen ceased. Filtration and
evaporation of the reaction solution gave an oil. It
was purified by flash chromatography (ether:hexane,
70:30 by volume, silica gel 230-400 mesh) to afford 35
10 as a colorless oil (230 mg, 96.2%). TLC only showed one
spot. 1H NMR ($CDCl_3$, 500 MHz) δ 7.22 (d, 2 H, $J=8$ Hz),
6.72 (d, 2 H, $J=8$ Hz), 6.59 (s, 1 H), 3.90 (s, 3 H),
3.88 (s, 3 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.63 (m, 1
H), 3.36 (m, 1 H), 3.26 (m, 1 H), 2.97 (m, 2 H). EIMS
15 m/e 314 (M^+ , 100). Anal. ($C_{19}H_{22}O_4$) C, H.

1-(4'-Methoxybenzyl)-5,6,7-
trimethoxyisoquinoline Methiodide (Takatonine Iodide
37). A solution of 36 (200 mg, 0.59 mmol) in anhydrous
decahydronaphthalene (5 mL) containing palladium black
20 (20 mg) was heated at reflux for 2 h under Ar. The
reaction mixture was filtered through a celite pad, and
the celite pad was rinsed with $CHCl_3$ (10 mL). After the
 $CHCl_3$ was evaporated, the residue was dissolved in ether
(10 mL), and MeI (0.5 mL) was added. The resulting
25 solution was kept at room temperature overnight. The
yellow crystalline precipitate was filtered and washed
with ether (5 mL) to give takatonine iodide (37) as
yellow plates (174.1 mg, 61.3%): m.p. 180-182°C; 1H NMR
($CDCl_3$, 200 MHz) δ 8.72 (d, br, 1 H, $J=6$ Hz), 8.32 (d, 1
30 H, $J=6$ Hz), 7.40 (s, 1 H), 7.01 (d, 2 H, $J=8$ Hz), 6.84
(d, 2 H, $J=8$ Hz), 5.11 (s, 2 H), 4.61 (s, 3 H), 4.14 (s,

1 3 H), 4.10 (s, 3 H), 4.01 (s, 3 H), 3.77 (s, 3 H). The
1 ¹H NMR spectrum of 6 was identical with the reported ¹H
NMR spectrum of takatonine iodide.

5 1-(4'-Methoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-
tetrahydroisoquinoline (38). Sodium borohydride (460
mg, 12.9 mmol) was added portionwise over a period of 30
min to a solution of 36 (460 mg, 1.36 mmol) in methanol
(5 mL) and the reaction solution was stirred at room
temperature for 1 h. The reaction solution was
10 evaporated under reduced pressure to dryness. The
residue was dissolved in water (5 mL) and basified with
ammonium hydroxide solution, then extracted with ether
(30, 20, and 10 mL). The combined ether layer was dried
over anhydrous sodium sulfate. Evaporation of the
15 filtrate and flash chromatography (ether, silica gel
230-400 mesh) gave compound 38 as an oil (450 mg,
96.0%): ¹H NMR (CDCl₃, 200 MHz) δ 7.18 (d, 2 H, J=8 Hz),
6.87 (d, 2 H, J=8 Hz), 6.49 (s, 1 H), 4.06 (m, 1 H),
3.86 (s, 3 H), 3.85 (s, 3 H), 3.81 (s, 3 H), 3.80 (s, 3
H), 3.16 (m, 2 H), 2.87 (m, 2 H), 2.68 (t, 2 H, J=6 Hz),
20 1.84 (s, br, 1 H); FABMS m/e 344 (MH⁺, 41).

1-(4'-Methoxybenzoyl)-5,6,7-trimethoxy-
isoquinoline (39). A solution of 36 (250 mg, 0.73 mmol)
and DDQ (188 mg, 0.81 mmol) in anhydrous THF (2 mL) was
heated at reflux overnight. Preparative TLC
25 purification (ether, precoated silica gel plate, 1000
microns) gave 39 as an oil (125 mg, 48.4%): IR (neat)
2924, 2851, 1659, 1560, 1475, 1260, 1159, 1122 cm⁻¹; ¹H
NMR (CDCl₃, 200 MHz) δ 8.48 (d, 1 H, J=6 Hz), 7.98 (d, 1
H, J=6 Hz), 7.95 (d, 2 H, J=8 Hz), 7.37 (s, 1 H), 6.96
30 (d, 2 H, J=8 Hz), 4.08 (s, 3 H), 4.03 (s, 3 H), 3.93 (s,

1 3 H), 3.88 (s, 3 H); CIMS (isobutane) m/e, 354 (MH⁺, 100).

5 1-(4'-Methoxybenzoyl)-5,6,7-trimethoxy-
isoquinoline Methiodide (40). A solution of 39 (70 mg,
0.2 mmol) in anhydrous benzene (2 mL) and iodomethane
(0.6 mL) was heated at reflux for 24 h under Ar. The
reaction mixture was evaporated to dryness and the
residue was partitioned between distilled water (10 mL)
and CHCl₃ (10 mL). The CHCl₃ was extracted with H₂O (2 x
10 5 mL), and the combined aqueous extracts were washed
with ether (5 mL). Evaporation of the distilled water
solution gave a yellow solid 40 (60 mg, 60.6%): ¹H NMR
(CDCl₃, 200 MHz) 8.95 (d, 1 H, J=6 Hz), 8.52 (d, 1 H,
J=6 Hz), 8.11 (d, br, 2 H, J=8 Hz), 7.10 (d, 2 H, J=8
15 Hz), 6.73 (s, 1 H), 4.53 (s, 3 H), 4.15 (s, 3 H), 4.14
(s, 3 H), 3.92 (s, 3 H), 3.80 (s, 3 H); FABMS calcd. for
C₂₁H₂₂INO: 368.1498 (cation). Found: 368.1489.

1-(4'-Methoxybenzyl)-5,6,7-trimethoxy-2-
methyl-1,2,3,4-tetrahydroisoquinoline
(Tetrahydrotakatonine, 41). A solution of 38 (400 mg,
20 1.2 mmol) in formic acetic anhydride (80 mL) was stirred
at room temperature overnight. A clear yellow solution
was obtained. The solvent was evaporated to dryness.
To this residue water (5 mL) was added, and the aqueous
solution was extracted with CH₂Cl₂ (20, 10, and 10 mL).
25 The CH₂Cl₂ layer was washed successively with 10% NaOH
solution (5 mL), water (5 mL), saturated aqueous NaCl (5
mL), and dried over anhydrous sodium sulfate.
Evaporation of the filtrate gave an oil (590 mg). A
solution of this oil (450 mg) in anhydrous toluene (10
30 mL) containing POCl₃ (2 mL) was heated at reflux for 3 h
under Ar. TLC showed that starting material was

1 consumed. After evaporation of the solvent, the
resulting brown residue was dissolved in methanol (30
mL). NaBH_4 (1.6 g) was added over 0.5 h, and the
reaction solution was stirred at room temperature for 2
5 h. Evaporation of the solvent gave a residue which was
extracted with CH_2Cl_2 (20, 10, and 10 mL). The organic
layer was washed successively with water (10 mL) and
saturated aqueous NaCl (10 mL) and dried over anhydrous
sodium sulfate. Evaporation of the filtrate and flash
10 chromatography (CHCl_3 , then CHCl_3 :EtOH, 96:4 by volume,
silica gel 230-400 mesh) gave 41 as an oil (225 mg,
52.5%): ^1H NMR (CDCl_3 , 200 MHz) δ 7.02 (d, 2 H, $J=8$ Hz),
6.80 (d, 2 H, $J=8$ Hz), 5.87 (s, 1 H), 3.84 (s, 3 H),
3.83 (s, 3 H), 3.78 (s, 3 H), 3.67 (t, 1 H, $J=6$ Hz),
3.55 (s, 3 H), 3.13 (m, 2 H), 2.75 (m, 4 H), 2.51 (s, 3
15 H); FABMS m/e 358 (MH^+ , 100). The ^1H NMR spectrum of 41
was consistent with the previously presented ^1H NMR of
tetrahydrotakatonine.

N-(2,3,4-trimethoxyphenethyl)acetamide (43).
20 Acetyl chloride (1.3 mL, 1.45 g, 18.2 mmol) was added
dropwise to a stirred suspension of compound 42 (3g,
12.1 mmol) in 2.0 N NaOH solution (27 mL, 54.0 mmol)
cooled in an ice bath. The resulting solution was
stirred at 0°C for 1 h. The reaction solution was
25 extracted with CHCl_3 (50, 30, and 20 mL) and the
combined CHCl_3 layer was washed with saturated NaCl
solution and dried over anhydrous Na_2SO_4 . Evaporation of
the filtrate gave a pale yellow oil that was subjected
to flash chromatography (ether, silica gel 230-400 mesh)
30 to give compound 43 as an oil (2.75 g, 89.9%): ^1H NMR
(CDCl_3 , 200 MHz) δ 6.83 (d, 1 H, $J=8$ Hz), 6.62 (d, 1 H,
 $J=8$ Hz), 5.84 (s, br, 1 H), 3.90 (s, 3 H), 3.87 (s, 3

1 H), 3.85 (s, 3 H), 3.44 (q, 2 H, J=6 Hz), 2.76 (t, 2 H, J=6 Hz), 1.93 (s, 3 H); EIMS m/e 253 (M⁺, 72).

1-Methyl-5,6,7-trimethoxy-3,4-dihydroisoquinoline (44). A solution of the acetamide 43 (280 mg, 1.1 mmol) in toluene (5 mL) containing POCl₃ (0.8 mL, 8.5 mmol) was heated at reflux under Ar for 2 h. The excess POCl₃ and the solvent were evaporated under vacuum. The black residue was washed with petroleum ether (10 mL). The residue was dissolved in distilled water (10 mL) and made basic by 5% NH₄OH aq (10 mL). The aqueous solution was extracted with CHCl₃ (20, 10, and 5 mL). The combined CHCl₃ layer was washed successively with water (10 mL) and saturated NaCl solution (10 mL) and dried over anhydrous Na₂SO₄. Evaporation of the filtrate and chromatography (ether:ethanol, 98:2 by volume, silica gel 230-400 mesh) gave compound 44 as a pale brown oil (230 mg, 89.2%): ¹H NMR (CDCl₃, 200 MHz) 6.84 (s, 1 H), 3.92 (s, 3 H), 3.89 (s, 3 H), 3.85 (s, 3 H), 3.61 (t, 2 H, J=8 Hz), 2.64 (t, 2 H, J=8 Hz), 2.36 (s, 3 H). EIMS m/e 235 (M⁺, 84).

2,5-Dimethoxybenzoyl Chloride (45). A mixture of 2,5-dimethoxybenzoic acid (25 g, 137.2 mmol) and thionyl chloride (35 mL, 470.6 mmol) was heated at reflux under Ar for 4 h. The reaction solution was evaporated to dryness and the residue was purified by high vacuum distillation at 127°C/2 mm Hg to give compound 45 as a pale yellow oil (26.5 g, 96.7%). When standing at room temperature, this oil changed to yellow crystals, m.p. 36-38°C.

2-(2',5'-Dimethoxybenzoyl)-1-methylene-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (46). A

1 solution of compound 45 (746 mg, 3.7 mmol) in anhydrous
benzene (2 mL) was slowly added at room temperature to a
solution of compound 44 (880 mg, 3.7 mmol) in anhydrous
benzene (10 mL) containing triethylamine (568 mg, 5.6
5 mmol, 0.78 mL). The resulting solution was heated at
reflux with stirring under Ar for 2 h. White NH_4Cl
precipitated and was removed by filtration. The
filtrate was evaporated to dryness and the residue was
subjected to flash chromatography (ether:triethylamine,
10 99:1 by volume, silica gel 230-300 mesh) to give
compound 46 as an oil (1.3 g, 87.8%): ^1H NMR (CDCl_3 , 200
MHz) δ 6.87 (s, 1 H), 6.85 (d, 1 H, $J=10$ Hz), 6.80 (d, 1
H, $J=3$ Hz), 6.70 (d, 1 H, $J=10$ Hz), 5.21 (s, br 1 H),
4.55 (s, br, 1 H), 3.90 (s, 6 H), 3.88 (s, 3 H), 3.84
15 (s, 3 H), 3.75 (s, 3 H), 3.41 (s, br, 2 H), 2.88 (t, 2
H, $J=6$ Hz). CIMS (isobutane) m/e 400 (MH^+ , 100).

5-Hydro-8-oxo-2,3,4,10-tetramethoxy-6H-
dibenzo-(a,g)quinolizine (47). A solution of compound
46 (1.59 g, 4.0 mmol) in methanol (500 mL) containing
triethylamine (0.5 mL) was irradiated with 450-W medium
20 pressure mercury lamp at room temperature for about 2 h
with stirring. Evaporation of the solvent gave a yellow
syrup that was subjected to flash chromatography (ether,
silica gel 230-400 mesh) to give a yellow solid.
Recrystallization of the solid from methanol gave
25 compound 47 as yellow needles (350 mg, 23.8%): m.p.
196-198°C; ^1H NMR (CDCl_3 , 200 MHz) δ 7.84 (d, 1 H, $J=4$
Hz), 7.51 (d, 1 H, $J=8$ Hz), 7.26 (d,d, 1 H, $J=8$ and 4
Hz), 7.09 (s, 1 H), 6.89 (s, 1 H), 4.34 (t, 2 H, $J=6$
Hz), 3.97 (s, 3 H), 3.94 (s, 6 H), 3.91 (s, 3 H), 2.96
30 (t, 2 H, $J=6$ Hz). CIMS (isobutane) m/e 368 (MH^+ , 100).
Anal. ($\text{C}_{21}\text{H}_{21}\text{NO}_5$): C, H.

1 5,8,13,13a-Tetrahydro-2,3,4,10-tetramethoxy-
6H-dibenzo-(a,g)quinolizine (48). A suspension of
LiAlH₄ (1.4 mL, 1.4 mmol, 5 eq, 1.0 M in THF) was added
dropwise to a solution of compound 47 (100 mg, 0.27
5 mmol) in anhydrous THF (15 mL) with stirring at room
temperature under Ar. The reaction mixture was stirred
under reflux for 2 h. A yellow solution developed. The
excess LiAlH₄ was decomposed by adding water until no
hydrogen bubbles appeared. The residue was extracted
10 with ether:THF (7:3 by volume, 30, 20 mL). The combined
organic layer was filtered through a glass wool pad, and
the filtrate was evaporated to dryness. The residue was
dissolved in fresh methanol (10 mL), and NaBH₄ (125 mg,
3.28 mmol) was added in several portions. The reaction
15 solution was stirred at reflux under Ar for 1.5 h. The
reaction was evaporated to dryness under vacuum. The
residue was dissolved in 10% HCl (5 mL), neutralized
with solid K₂CO₃ to pH 8, extracted with CHCl₃ (20, 10,
10 mL), and dried over anhydrous Na₂SO₄. Evaporation of
20 the filtrate obtained after removal of the Na₂SO₄ gave a
pale yellow oil. Preparative silica gel TLC (ether,
silica gel precoated plate, 1000 microns) purification
gave compound 48 (92 mg, 95.1%). Recrystallization of
compound 48 from methanol gave pale yellow needles (22.0
mg), m.p. 104-106°C: ¹H NMR (CDCl₃, 200 MHz) 57.07 (d, 1
25 H, J=8 Hz), 6.75 (dd, 1 H, J=8 and 2 Hz), 6.62 (d, 1 H,
J=2 Hz), 6.57 (s, 1 H), 3.88 (s, 6 H), 3.87 (s, 3 H),
3.79 (s, 3 H), 3.79 (m, 3 H), 3.21 (m, 2 H), 2.85 (m, 3
H), 2.52 (m, 1 H). FABMS (Glycerol) m/e 356 (MH⁺, 47).
30 Anal. (C₂₁H₂₅NO₄): C, H.

The above preferred embodiments and examples
are given to illustrate the scope and spirit of the

1 present invention. These embodiments and examples will
make apparent to those skilled in the art other
embodiments and examples. These other embodiments are
also examples within the contemplation of the present
5 invention. Therefore, the present invention should be
limited only by the appended claims.

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1 WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound having the formula:



and pharmaceutically acceptable salts thereof, wherein:

Ar and Ar₁ are independently aryl or heteroaryl; and Ar may be mono, di, tri, or tetrasubstituted with R' and Ar₁ may be mono, di, tri, or tetrasubstituted with R'';

10 X is -C-, -NH-CH₂-, -CH₂NH-, -NH-C-, -C-NH-,

$$\begin{array}{ccccccc} & & \parallel & & \parallel & & \parallel \\ & & O & & O & & O \end{array}$$

 - (Y₂)(Y₃)C-C(Z₂)(Z₃)- or cis or trans ethylene radical of the formula -(Y₁)C=C(Z₁), CH₂, or CHOH;

Y₁, Y₂, Y₃, Z₁, Z₂ and Z₃ are independently hydrogen, lower alkyl, lower alkoxy, carboxy, lower carbalkoxy, COONR₁₃R₁₄, cyano, or COOQNR₁₅R₁₆;

20 R₁₃, R₁₄, R₁₅ and R₁₆ are independently hydrogen or lower alkyl;

Q is lower alkylene;

each R' may be the same or different and consists of R₁, R₂, R₃ and R₄, and each R'' may be the

25 same or different and consists of R₅, R₆, R₇ and R₈;

R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ are independently hydrogen, lower alkyl, halo, amino, lower alkylamino, diloweralkylamino, lower alkoxy, lower arylalkoxy, cyano, aryloxy, mercapto, lower alkyl thio, amino lower alkyl, carboxy, carbolower alkoxy, CONHR₉, NHCO(R₉), lower alkanoyl, nitro, CF₃, lower alkyl carbonyloxy, amino lower alkoxy, lower alkyl amino lower

1 alkoxy, dilower alkylamino lower alkoxy, aminolower
alkylene oxycarbonyl, lower alkylamino loweralkyleneoxy
carbonyl, dilower alkylamino lower alkylene oxy
carbonyl, OSi(R₁₀R₁₁R₁₂) or Si(R₁₇)(R₁₈)(R₁₉) and at least
5 two or R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ is loweralkoxy;

R₉ is hydrogen or lower alkyl;
R₁₀, R₁₁, R₁₇, R₁₈ and R₁₉ are independently lower
10 alkyl; R₁₂ is lower alkyl or lower alkoxy; and a
pharmaceutical carrier therefor.

2. The pharmaceutical composition according
to Claim 1 wherein Ar and Ar₁ are independently aryl.

3. The pharmaceutical composition of Claim 1
15 wherein X is -NHCH₂-, -CH₂NH-, -C-NH-, -NH-C-, or cis or

$$\begin{array}{c} \parallel \\ \text{O} \end{array} \qquad \begin{array}{c} \parallel \\ \text{O} \end{array}$$

trans -(Y₁)C=C(Z₁).

4. The pharmaceutical composition of Claim 1
wherein X is -NHCH₂-, -CH₂NH-, -C-NH-, -NH-C-, or cis
20
$$\begin{array}{c} \parallel \\ \text{O} \end{array} \qquad \begin{array}{c} \parallel \\ \text{O} \end{array}$$

(Y₁)C=C(Z₁).

5. The pharmaceutical composition according
to Claim 1 wherein Y₁, Y₂, Y₃, Z₁, Z₂ and Z₃ are hydrogen.

6. The pharmaceutical composition according
25 to Claim 1 wherein lower alkoxy is alkoxy having 1-4
carbon atoms.

7. The pharmaceutical composition according
to Claim 6 wherein lower alkoxy is methoxy.

8. The pharmaceutical composition according
30 to Claim 1 where at least three of R₁, R₂, R₃, R₄, R₅, R₆,
R₇ and R₈ are lower alkoxy.

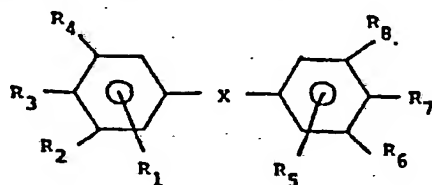
1 9. The pharmaceutical composition according
to Claim 1 wherein three of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , and
 R_8 are lower alkoxy.

10. The pharmaceutical composition according
to Claim 1 wherein R_1 and R_5 are hydrogen.

5 11. The pharmaceutical composition according
to Claim 1 wherein R_1 and R_5 are hydrogen and R_2 , R_3 and
 R_4 are lower alkoxy.

12. The pharmaceutical composition according
to Claim 1 wherein R_1 and R_5 are hydrogen, R_2 , R_3 and R_4
10 are lower alkoxy and R_7 is lower alkoxy, hydrogen, halo,
amino, lower alkylamino, diloweralkylamino or lower
alkylthio.

13. The pharmaceutical composition according
to Claim 1 having the formula:



20 and pharmaceutically acceptable salts thereof, wherein:

X is $\text{-}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{-}$, $\text{-NH-CH}_2\text{-}$, $\text{-CH}_2\text{NH-}$, $\text{-NH-}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{-}$, $\text{-C-}\overset{\text{O}}{\underset{\text{O}}{\text{NH}}}\text{-}$,

25 $\text{-(Y}_2\text{)(Y}_3\text{)C-C(Z}_2\text{)(Z}_3\text{)-}$ or cis or trans ethylene radical of
the formula $\text{-(Y}_1\text{)C=C(Z}_1\text{)}$, CH_2 or CHOH ;

Y_1 , Y_2 , Y_3 , Z_1 , Z_2 and Z_3 are independently
hydrogen, lower alkyl, lower alkoxy, carboxy, lower
carbalkoxy, $\text{COONR}_{13}\text{R}_{14}$, cyano, or $\text{COOQNR}_{15}\text{R}_{16}$;

30 R_{13} , R_{14} , R_{15} and R_{16} are independently hydrogen
or lower alkyl;

Q is lower alkylene;

- 1 each R' may be the same or different and
 consists of R₁, R₂, R₃ and R₄, each R'' may be the same or
 different and consists of R₅, R₆, R₇ and R₈;
 5 R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ are
 independently hydrogen, lower alkyl, halo, amino, lower
 alkylamino, diloweralkylamino, lower alkoxy, lower
 aryalkoxy, cyano, aryloxy, mercapto, lower alkyl thio,
 amino lower alkyl, carboxy, carbolower alkoxy, CONHR₉,
 10 NHCO(R₉), lower alkanoyl, nitro, CF₃, lower alkyl
 carbonyloxy, amino lower alkoxy, lower alkyl amino lower
 alkoxy, dilower alkylamino lower alkoxy, aminolower
 alkylene oxycarbonyl, lower alkylamino loweralkyleneoxy
 carbonyl, dilower alkylamino lower alkylene oxy
 carbonyl, OSi(R₁₀R₁₁R₁₂) or Si(R₁₇)(R₁₈)(R₁₉) and at least
 15 two or R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ is loweralkoxy;
 R₉ is hydrogen or lower alkyl;
 R₁₀, R₁₁, R₁₂, R₁₇, R₁₈ and R₁₉ are independently
 lower alkyl.
14. The pharmaceutical composition according
 20 to Claim 13 wherein X is $-\text{NH}-\text{CH}_2-$, $-\text{CH}_2-\text{NH}-$, $-\text{NH}-\text{C}-$, $-\text{C}-$

$$\begin{array}{c} \parallel \\ \text{O} \end{array}$$

$$\begin{array}{c} \parallel \\ \text{O} \end{array}$$

 NH-, or cis or trans $-(\text{Y}_1)\text{C}=\text{C}(\text{Z}_1)$.
15. The pharmaceutical composition according
 to Claim 13 wherein Y₁, Y₂, Y₃, Z₁, Z₂ and Z₃ are
 25 hydrogen.
16. The pharmaceutical composition according
 to Claim 13 wherein lower alkoxy is alkoxy having 1-4
 carbon atoms.
17. The pharmaceutical composition according
 30 to Claim 16 wherein lower alkoxy is methoxy.

1 18. The pharmaceutical composition according
to Claim 13 where at least three of R_1 , R_2 , R_3 , R_4 , R_5 ,
 R_6 , R_7 , and R_8 are lower alkoxy.

5 19. The pharmaceutical composition according
to Claim 13 wherein three of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , and
 R_8 are lower alkoxy.

20. The pharmaceutical composition according
to Claim 13 wherein R_1 and R_5 are hydrogen.

10 21. The pharmaceutical composition of Claim 19
wherein at least three of R_1 , R_2 , R_3 , and R_4 are lower
alkoxy.

22. The pharmaceutical composition according
to Claim 13 wherein R_1 and R_5 are hydrogen and R_2 , R_3 , and
 R_4 are lower alkoxy.

15 23. The pharmaceutical composition according
to Claim 13 wherein R_1 and R_5 are hydrogen, R_2 , R_3 , and R_4
are lower alkoxy and R_7 is lower alkoxy, hydrogen, halo,
amino, lower alkylamino, dilower alkylamino or lower
alkyl thio.

20 24. The pharmaceutical composition according
to Claim 13 wherein X is -C- .



25. The pharmaceutical composition according
to Claim 24 wherein R_1 and R_5 are hydrogen.

25 26. The pharmaceutical composition according
to Claim 25 wherein R_1 and R_5 are hydrogen and R_2 , R_3 , R_4 ,
 R_6 , R_7 , and R_8 are independently lower alkoxy, hydrogen or
lower alkyl.

30 27. The pharmaceutical composition according
to Claim 24 wherein R_2 , R_3 , R_4 , R_6 , R_7 , and R_8 are
independently lower alkoxy or hydrogen.

1 28. The pharmaceutical composition according
to Claim 24 wherein R_2 , R_3 and R_4 are lower alkoxy and R_7
is lower alkoxy.

5 29. The pharmaceutical composition according
to Claim 24 wherein lower alkoxy is methoxy.

30. The pharmaceutical composition according
to Claim 13 wherein X is CHOH;

10 R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are
independently hydrogen, lower alkyl, halo, amino, lower
alkylamino, diloweralkylamino, lower alkoxy, lower
arylalkoxy, cyano, aryloxy, mercapto, lower alkyl thio,
amino lower alkyl, carboxy, carbolower alkoxy, CONHR₉,
NHCO(R_9), lower alkanoyl, nitro, CF₃, lower alkyl
carbonyloxy, amino lower alkoxy, lower alkyl amino lower
15 alkoxy, dilower alkylamino lower alkoxy, aminolower
alkylene oxycarbonyl, lower alkylamino loweralkyleneoxy
carbonyl, dilower alkylamino lower alkylene oxy
carbonyl, OSi(R_{10} R_{11} R_{12}) or Si(R_{17})(R_{18})(R_{19}) and at least
two of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 is loweralkoxy;

20 R_9 is hydrogen or lower alkyl;

R_{10} , R_{11} , R_{17} , R_{18} and R_{19} are independently lower
alkyl; R_{12} is lower alkyl or lower alkoxy.

31. The pharmaceutical composition according
to Claim 30 wherein lower alkoxy is methoxy.

25 32. The pharmaceutical composition according
to Claim 30 wherein R_1 and R_5 are hydrogen.

33. The pharmaceutical composition according
to Claim 30 wherein R_1 and R_5 are hydrogen and R_2 , R_3 , R_4 ,
 R_6 , R_7 and R_8 are independently lower alkoxy, hydrogen or
lower alkyl.
30

1 34. The pharmaceutical composition according
to Claim 30 wherein R_2 , R_3 , R_4 , R_6 , R_7 and R_8 are
independently lower alkoxy or hydrogen.

5 35. The pharmaceutical composition according
to Claim 13 wherein X is CH_2 ;

R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are
independently hydrogen, lower alkyl, halo, amino, lower
alkylamino, diloweralkylamino, lower alkoxy, lower
arylalkoxy, cyano, aryloxy, mercapto, lower alkyl thio,
10 amino lower alkyl, carboxy, carbolower alkoxy, CONHR_9 ,
 $\text{NHCO}(R_9)$, lower alkanoyl, nitro, CF_3 , lower alkyl
carbonyloxy, amino lower alkoxy, lower alkyl amino lower
alkoxy, dilower alkylamino lower alkoxy, aminolower
alkylene oxycarbonyl, lower alkylamino loweralkyleneoxy
carbonyl, dilower alkylamino lower alkylene oxy
15 carbonyl, $\text{OSi}(R_{10}R_{11}R_{12})$ or $\text{Si}(R_{17})(R_{18})(R_{19})$ and at least
two of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 is loweralkoxy;

R_9 is hydrogen or lower alkyl;

R_{10} , R_{11} , R_{17} , R_{18} and R_{19} are independently lower
alkyl; R_{12} is lower alkyl or lower alkoxy.

20 36. The pharmaceutical composition according
to Claim 35 wherein lower alkoxy is methoxy.

 37. The pharmaceutical composition according
to Claim 35 wherein R_1 and R_5 are hydrogen.

25 38. The pharmaceutical composition according
to Claim 35 wherein R_1 and R_5 are hydrogen and R_2 , R_3 , R_4 ,
 R_6 , R_7 and R_8 are independently lower alkoxy, hydrogen or
lower alkyl.

30 39. The pharmaceutical composition according
to Claim 35 wherein R_2 , R_3 , R_4 , R_6 , R_7 and R_8 are
independently lower alkoxy or hydrogen.

1 40. The pharmaceutical composition according
to Claim 13 wherein X is NH-CH_2 or CH_2NH ;

5 $\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5, \text{R}_6, \text{R}_7$ and R_8 are
independently hydrogen, lower alkyl, halo, amino, lower
alkylamino, diloweralkylamino, lower alkoxy, lower
10 arylalkoxy, cyano, aryloxy, mercapto, lower alkyl thio,
aminolower alkyl, carboxy, carbolower, alkoxy, CONHR_9 ,
 $\text{NHCO}(\text{R}_9)$, lower alkanoyl, nitro, CF_3 , lower alkyl
carbonyloxy, amino lower alkoxy, lower alkyl amino lower
alkoxy, dilower alkylamino lower alkoxy, aminolower
15 alkylene oxycarbonyl, lower alkylamino loweralkyleneoxy
carboxy, dilower alkylamino lower alkylene oxy carbonyl,
 $\text{OSi}(\text{R}_{10}, \text{R}_{11}, \text{R}_{12})$ or $\text{Si}(\text{R}_{17})(\text{R}_{18})(\text{R}_{19})$, at least two of $\text{R}_1, \text{R}_2,$
 $\text{R}_3, \text{R}_4, \text{R}_5, \text{R}_6, \text{R}_7$ and R_8 is lower alkoxy;

15 R_9 is hydrogen or lower alkyl;

15 $\text{R}_{10}, \text{R}_{11}, \text{R}_{17}, \text{R}_{18}$ and R_{19} are independently lower
alkyl; R_{12} is lower alkyl or lower alkoxy; and a
pharmaceutical carrier therefor.

20 41. The pharmaceutical composition according
to Claim 40 wherein X is CH_2NH .

20 42. The pharmaceutical composition of Claim 40
wherein at least three of $\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5, \text{R}_6, \text{R}_7$ or R_8
are lower alkoxy.

25 43. The pharmaceutical composition according
to Claim 42 wherein three of $\text{R}_1, \text{R}_2, \text{R}_3$ or R_4 are lower
alkoxy.

25 44. The pharmaceutical composition according
to Claim 43 wherein R_2, R_3 and R_4 are lower alkoxy.

30 45. The pharmaceutical composition according
to Claim 40 wherein R_1, R_2 and R_4 are independently
hydrogen or lower alkoxy;

- 1 R_3 is hydrogen, lower alkoxy, arylalkoxy,
loweralkyl carbonyloxy or $\text{OSi}(R_{10}R_{11}R_{12})$;
 R_5 is hydrogen, halo or lower alkoxy;
 R_6 and R_8 are independently hydrogen or lower
5 alkoxy;
 R_7 is hydrogen, lower alkoxy, lower alkyl,
halo, lower alkyl carbonyloxy, $\text{OSi}(R_{10}R_{11}R_{12})$,
 $\text{Si}(R_{17})(R_{18})(R_{19})$, amino,
10 lower alkylamino, dilower alkylamino, $\text{NHC}-R_9$,
diloweralkylamino lower alkoxy, lower alkylthio,
mercapto or nitro;
 R_{10} , R_{11} , R_{12} , R_{17} , R_{18} and R_{19} are independently
lower alkyl; and
15 R_9 is lower alkyl or hydrogen.
46. The pharmaceutical composition according
to Claim 40 wherein lower alkoxy is methoxy.
47. The pharmaceutical composition according
to Claim 40 wherein R_1 and R_5 are hydrogen.
20 48. The pharmaceutical composition according
to Claim 40 wherein R_1 and R_5 are hydrogen and R_2 , R_3 , R_4 ,
 R_6 , R_7 and R_8 are hydrogen or lower alkoxy.
49. The pharmaceutical composition according
to Claim 48 wherein R_2 , R_3 and R_4 are lower alkoxy.
25 50. The pharmaceutical composition according
to Claim 48 wherein lower alkoxy is methoxy.
51. The pharmaceutical composition according
to Claim 49 wherein lower alkoxy is methoxy.
52. The pharmaceutical composition according
30 to Claim 13 wherein X is $-\text{CONH}-$ or $-\text{NHCO}-$;
 R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are
independently

1 hydrogen, lower alkyl, halo amino, lower alkylamino,
diloweralkylamino, lower alkoxy, lower aryalkoxy, cyano,
aryloxy, mercapto, lower alkyl thio, amino lower alkyl,
5 carboxy, carbolower alkoxy, CONHR_9 , $\text{NHCO}(\text{R}_9)$, lower
alkanoyl, nitro, CF_3 , lower alkyl carbonyloxy, amino
lower alkoxy, lower alkyl amino lower alkoxy, dilower
alkylamino lower alkoxy, aminolower alkylene
oxycarbonyl, lower alkylamino loweralkyleneoxy carbonyl,
dilower alkylamino lower alkylene oxy carbonyl,
10 $\text{OSi}(\text{R}_{10}\text{R}_{11}\text{R}_{12})$ or $\text{Si}(\text{R}_{17})(\text{R}_{18})(\text{R}_{19})$ and at least two of R_1 ,
 R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 is loweralkoxy;
 R_9 is hydrogen or lower alkyl;
 R_{10} , R_{11} , R_{12} , R_{17} , R_{18} and R_{19} are independently
lower alkyl.

15 53. The pharmaceutical composition according
to Claim 52 wherein X is $-\text{CONH}-$;

R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are
independently
hydrogen, lower alkyl, halo amino, lower alkylamino,
diloweralkylamino, lower alkoxy, lower aryalkoxy, cyano,
20 aryloxy, mercapto, lower alkyl thio, amino lower alkyl,
carboxy, carbolower alkoxy, CONHR_9 , $\text{NHCO}(\text{R}_9)$, lower
alkanoyl, nitro, CF_3 , lower alkyl carbonyloxy, amino
lower alkoxy, lower alkyl amino lower alkoxy, dilower
alkylamino lower alkoxy, aminolower alkylene
25 oxycarbonyl, lower alkylamino loweralkyleneoxy carbonyl,
dilower alkylamino lower alkylene oxy carbonyl,
 $\text{OSi}(\text{R}_{10}\text{R}_{11}\text{R}_{12})$ or $\text{Si}(\text{R}_{17})(\text{R}_{18})(\text{R}_{19})$ and at least two of R_1 ,
 R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 is loweralkoxy;
 R_9 is hydrogen or lower alkyl;
30 R_{10} , R_{11} , R_{12} , R_{17} , R_{18} and R_{19} are independently
lower alkyl.

1 54. The pharmaceutical composition of Claim 53
wherein at least three of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , or R_8
are lower alkoxy.

5 55. The pharmaceutical composition according
to Claim 54 wherein three of R_1 , R_2 , R_3 or R_4 are lower
alkoxy.

56. The pharmaceutical composition according
to Claim 55 wherein R_2 , R_3 and R_4 are lower alkoxy.

10 57. The pharmaceutical composition according
to Claim 52 wherein R_1 , R_2 and R_4 are independently
hydrogen or lower alkoxy;

R_3 is hydrogen, lower alkoxy, arylalkoxy,
loweralkyl carbonyloxy or $\text{OSi}(R_{10}R_{11}R_{12})$;

R_5 is hydrogen, halo or lower alkoxy;

15 R_6 and R_8 are independently hydrogen or lower
alkoxy;

R_7 is hydrogen, lower alkoxy, lower alkyl,
halo, lower alkyl carbonyloxy, $\text{OSi}(R_{10}R_{11}R_{12})$,
 $\text{Si}(R_{17})(R_{18})(R_{19})$, amino,

20 lower alkylamino, dilower alkylamino, $\text{NHC}-R_9$,
diloweralkylamino lower alkoxy, lower alkylthio,
mercapto or nitro;

25 R_{10} , R_{11} , R_{12} , R_{17} , R_{18} and R_{19} are independently
lower alkyl; and

R_9 is lower alkyl or hydrogen.

58. The pharmaceutical composition according
to Claim 52 wherein lower alkoxy is methoxy.

30 59. The pharmaceutical composition according
to Claim 52 wherein R_1 and R_5 are hydrogen.

1 60. The pharmaceutical composition according
to Claim 52 wherein R_1 and R_5 are hydrogen and R_2 , R_3 , R_4 ,
 R_6 , R_7 and R_8 are hydrogen or lower alkoxy.

5 61. The pharmaceutical composition according
to Claim 60 wherein R_2 , R_3 and R_4 are lower alkoxy.

 62. The pharmaceutical composition according
to Claim 60 wherein lower alkoxy is methoxy.

 63. The pharmaceutical composition according
to Claim 61 wherein lower alkoxy is methoxy.

10 64. The pharmaceutical composition according
to Claim 13 wherein X is $-(Y_2)(Y_3)C-C(Z_2)(Z_3)-$ wherein
 R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are
independently hydrogen, lower alkyl, halo, amino, lower
alkylamino, diloweralkylamino, lower alkoxy, lower
15 arylalkoxy, cyano, aryloxy, mercapto, lower alkyl thio,
amino lower alkyl, carboxy, carbolower alkoxy, $CONHR_9$,
 $NHCO(R_9)$, lower alkanoyl, nitro, CF_3 , lower alkyl
carbonyloxy, amino lower alkoxy, lower alkyl amino lower
alkoxy, dilower alkylamino lower alkoxy, lower alkylene
20 oxycarbonyl, lower alkylamino loweralkyleneoxy
carbonyl, $OSi(R_{10}R_{11}R_{12})$ or $Si(R_{17})(R_{18})(R_{19})$ and at least
two of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 is loweralkoxy;
 R_9 is hydrogen or lower alkyl;
 R_{10} , R_{11} , R_{12} , R_{17} , R_{18} and R_{19} are independently
25 lower alkyl.

 65. The pharmaceutical composition according
to Claim 64 wherein Y_2 and Z_2 are hydrogen.

30 66. The pharmaceutical composition according
to Claim 64 wherein Y_2 and Z_2 are hydrogen and Y_3 and Z_3
are independently hydrogen, cyano or lower carbalkoxy.

1 67. The pharmaceutical composition according
to Claim 64 wherein Y_2 and Z_2 are hydrogen, Y_3 is
hydrogen or cyano and Z_3 is hydrogen, cyano or lower
carbalkoxy;

5 $R_1, R_2, R_3, R_4, R_5, R_6, R_7$ and R_8 are
independently hydrogen, lower alkyl, halo, amino, lower
alkylamino, diloweralkylamino, lower alkoxy, lower
arylkoxy, cyano, aryloxy, mercapto, lower alkyl thio,
amino lower alkyl, carboxy, carbolower alkoxy, $CONHR_9$,
10 $NHCO(R_9)$, lower alkanoyl, nitro, CF_3 , lower alkyl
carbonyloxy, amino lower alkoxy, lower alkyl amino lower
alkoxy, dilower alkylamino lower alkoxy, amino lower
alkylene oxycarbonyl, lower alkylamino loweralkyleneoxy
carbonyl, dilower alkylamino lower alkylene oxycarbonyl,
15 $OSi(R_{10}R_{11}R_{12})$ or $Si(R_{17})(R_{18})(R_{19})$ and at least two of R_1 ,
 $R_2, R_3, R_4, R_5, R_6, R_7$ and R_8 is loweralkoxy;

R_9 is hydrogen or lower alkyl;

$R_{10}, R_{11}, R_{12}, R_{17}, R_{18}$ and R_{19} are independently
lower alkyl.

20 68. The pharmaceutical composition according
to Claim 67 wherein Z_3 and Y_3 are hydrogen;

$R_1, R_2, R_3, R_4, R_5, R_6, R_7$ and R_8 are
independently hydrogen, lower alkyl, halo, amino, lower
alkylamino, diloweralkylamino, lower alkoxy, lower
arylalkoxy, cyano, aryloxy, mercapto, lower alkyl thio,
25 amino lower alkyl, carboxy, carbolower alkoxy, $CONHR_9$,
 $NHCO(R_9)$, lower alkanoyl, nitro, CF_3 , lower alkyl
carbonyloxy, amino lower alkoxy, lower alkyl amino lower
alkoxy, dilower alkylamino lower alkoxy, amino lower
alkylene oxycarbonyl, lower alkylaminoloweralkyleneoxy
30 carbonyl, dilower alkylamino lower alkylene oxy

1 carbonyl, $\text{OSi}(\text{R}_{10}\text{R}_{11}\text{R}_{12})$ or $\text{Si}(\text{R}_{17})(\text{R}_{18})(\text{R}_{19})$ and at least
 two or $\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5, \text{R}_6, \text{R}_7$ and R_8 is loweralkoxy;
 R_9 is hydrogen or lower alkyl; and
 $\text{R}_{10}, \text{R}_{11}, \text{R}_{12}, \text{R}_{17}, \text{R}_{18}$ and R_{19} are independently
 5 lower alkyl.

69. The pharmaceutical composition of Claims
 64, 67 or 68 wherein at least three of $\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5,$
 R_6, R_7 or R_8 are lower alkoxy.

70. The pharmaceutical composition according
 to Claim 69 wherein three of $\text{R}_1, \text{R}_2, \text{R}_3$ or R_4 are lower
 10 alkoxy.

71. The pharmaceutical composition according
 to Claim 70 wherein R_2, R_3 and R_4 are lower alkoxy.

72. The pharmaceutical composition according
 to Claims 68, 69 or 71 wherein R_1, R_2 and R_4 are
 15 independently hydrogen or lower alkoxy;

R_3 is hydrogen, lower alkoxy, arylalkoxy,
 loweralkyl carbonyloxy or $\text{OSi}(\text{R}_{10}\text{R}_{11}\text{R}_{12})$;

R_5 is hydrogen, halo or lower alkoxy;

20 R_6 and R_8 are independently hydrogen or lower
 alkoxy;

R_7 is hydrogen, lower alkoxy, lower alkyl,
 halo, lower alkyl carbonyloxy, $\text{OSi}(\text{R}_{10}\text{R}_{11}\text{R}_{12}),$
 $\text{Si}(\text{R}_{17})(\text{R}_{18})(\text{R}_{19}),$ amino,

25 lower alkylamino, dilower alkylamino, $\text{NHC}-\text{R}_9,$
 diloweralkylamino lower alkoxy, lower alkylthio,
 mercapto or nitro;

$\text{R}_{10}, \text{R}_{11}, \text{R}_{12}, \text{R}_{17}, \text{R}_{18}$ and R_{19} are independently
 30 lower alkyl; and

R_9 is lower alkyl or hydrogen.

1 73. The pharmaceutical composition according to Claim 72 wherein lower alkoxy is methoxy.

74. The pharmaceutical composition according to Claims 64, 67 or 68 wherein R_1 and R_5 are hydrogen.

5 75. The pharmaceutical composition according to Claims 64, 67 or 68 wherein R_3 , R_6 , R_7 and R_8 are independently hydrogen, lower alkoxy, thio alkyl, amino, lower alkylamino, diloweralkylamino, loweralkyl carbonyloxy, aminoalkoxy, lower alkylamino carbonyloxy or dilower alkylamino carbonyloxy.

10 76. The pharmaceutical composition according to Claim 75 wherein R_5 is hydrogen and one of R_6 , R_7 and R_8 is lower alkoxy, loweralkylamino or diloweralkylamino.

15 77. The pharmaceutical composition according to Claim 76 wherein R_7 is lower alkoxy, lower alkylamino or diloweralkylamino.

78. The pharmaceutical composition according to Claim 13 wherein X is cis or trans $(Y_1)C=C(Z_1)$,

20 Y_1 and Z_1 are independently hydrogen, lower alkyl, lower alkoxy, carboxy, lower carbalkoxy, $COONR_{13}R_{14}$, cyano, or $COOQNR_{15}R_{16}$;

R_{13} , R_{14} , R_{15} and R_{16} are independently hydrogen or lower alkyl;

Q is lower alkylene;

25 R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are independently hydrogen, lower alkyl, halo, amino, lower alkylamino, diloweralkylamino, lower alkoxy, lower arylalkoxy, cyano, aryloxy, mercapto, lower alkyl thio, amino lower alkyl, carboxy, carbolower alkoxy, $CONHR_9$,
30 $NHCO(R_9)$, lower alkanoyl, nitro, CF_3 , lower alkyl carbonyloxy, amino lower alkoxy, lower alkyl amino lower

1 alkoxy, dilower alkylamino lower alkoxy, amino lower
alkylene oxycarbonyl, lower alkylamino loweralkyleneoxy
carbonyl, dilower alkylamino lower alkylene oxy
carbonyl, $\text{OSi}(\text{R}_{10}\text{R}_{11}\text{R}_{12})$ or $\text{Si}(\text{R}_{17})(\text{R}_{18})(\text{R}_{19})$ and at least
5 two or $\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5, \text{R}_6, \text{R}_7$ and R_8 is loweralkoxy;
 R_9 is hydrogen or lower alkyl; and
 $\text{R}_{10}, \text{R}_{11}, \text{R}_{12}, \text{R}_{17}, \text{R}_{18}$ and R_{19} are independently
lower alkyl.

79. The pharmaceutical composition according
to Claim 78 wherein at least one of Y and Z is hydrogen.

80. The pharmaceutical composition of Claim 79
wherein Y is $\text{COOH}, \text{COOMe}, \text{CONHMe}, \text{COONHET}, \text{COO}(\text{CH}_2)\text{Net}_2,$
 $\text{COO}(\text{CH}_2)_2\text{NMe}_2$ or hydrogen and Z is hydrogen or COOH .

81. The pharmaceutical composition according
to Claim 78 wherein at least three of $\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5,$
15 R_6, R_7 or R_8 is lower alkoxy.

82. The pharmaceutical composition according
to Claim 81 wherein at most six of $\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5, \text{R}_6,$
 R_7 or R_8 is lower alkoxy.

83. The pharmaceutical composition of Claim 81
20 wherein three of $\text{R}_1, \text{R}_2, \text{R}_3$ or R_4 are lower alkoxy.

84. The pharmaceutical composition according
to Claim 81 wherein R_1 is hydrogen and $\text{R}_2, \text{R}_3,$ and R_4 are
lower alkoxy.

85. The pharmaceutical composition according
to Claim 78 wherein R_1, R_2 and R_4 are independently
25 hydrogen or lower alkoxy;

R_3 is hydrogen, lower alkoxy, arylalkoxy,
loweralkyl carbonyloxy or $\text{OSi}(\text{R}_{10}\text{R}_{11}\text{R}_{12});$

R_5 is hydrogen, halo or lower alkoxy;

30 R_6 and R_8 are independently hydrogen or lower
alkoxy;

1 R_7 is hydrogen, lower alkoxy, lower alkyl,
halo, lower alkyl carbonyloxy, $\text{OSi}(R_{10}R_{11}R_{12})$,
 $\text{Si}(R_{17})(R_{18})(R_{19})$, amino,

5 lower alkylamino, dilower alkylamino, $\text{NHC}-R_9$,
diloweralkylamino lower alkoxy, lower alkylthio,
mercapto or nitro;

R_{10} , R_{11} , R_{12} , R_{17} , R_{18} and R_{19} are independently
lower alkyl; and

10 R_9 is lower alkyl or hydrogen.

86. The pharmaceutical composition according
to Claim 78 wherein R_1 and R_5 are hydrogen.

87. The pharmaceutical composition according
to Claim 78 wherein R_1 and R_5 are hydrogen and R_2 , R_3 and
15 R_4 are lower alkoxy.

88. The pharmaceutical composition according
to Claim 78 wherein R_1 and R_5 are hydrogen, R_2 , R_3 and R_4
are lower alkoxy and R_6 , R_7 and R_8 are independently
hydrogen, lower alkoxy, halo, amino, lower alkylamino,
20 dilower alkylamino, lower alkyl thio or lower alkyl.

89. The pharmaceutical composition according
to Claim 88 wherein R_1 , R_5 , R_6 and R_8 are hydrogen, R_4 , R_3
and R_7 are independently lower alkoxy and R_2 is hydrogen,
lower alkoxy, halo, amino, lower alkylamino, dilower
25 alkylamino, lower alkyl thio or lower alkyl.

90. The pharmaceutical composition according
to Claims 88 or 89 wherein lower alkyl and lower alkoxy
contain 1-3 carbon atoms.

91. The pharmaceutical composition according
to Claims 88 or 89 wherein lower alkyl is methyl and
30 lower alkoxy is methoxy.

1 92. The pharmaceutical composition according
to Claim 78 wherein X is cis (Y₁)C=C(Z₁),

 Y₁ and Z₁ are independently hydrogen, lower
alkyl, lower alkoxy, carboxy, lower carbalkoxy,
5 COONR₁₃R₁₄, cyano, or COOQNR₁₅R₁₆;

 R₁₃, R₁₄, R₁₅ and R₁₆ are independently hydrogen
or lower alkyl;

 Q is lower alkylene;

 R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ are
10 independently hydrogen, lower alkyl, halo, amino, lower
alkylamino, diloweralkylamino, lower alkoxy, lower
arylalkoxy, cyano, aryloxy, mercapto, lower alkyl thio,
amino lower alkyl, carboxy, carbolower alkoxy, CONHR₉,
NHCO(R₉), lower alkanoyl, nitro, CF₃, lower alkyl
15 carbonyloxy, amino lower alkoxy, lower alkyl amino lower
alkoxy, dilower alkylamino lower alkoxy, amino lower
alkylene oxycarbonyl, lower alkylamino loweralkyleneoxy
carbonyl, dilower alkylamino lower alkylene oxy
carbonyl, OSi(R₁₀R₁₁R₁₂) or Si(R₁₇)(R₁₈)(R₁₉) and at least
20 two or R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ is loweralkoxy;

 R₉ is hydrogen or lower alkyl; and

 R₁₀, R₁₁, R₁₂, R₁₇, R₁₈ and R₁₉ are independently
lower alkyl.

 93. The pharmaceutical composition according
to Claim 92 wherein at least one of Y and Z is hydrogen.

25 94. The pharmaceutical composition of Claim 92
wherein Y is COOH, COOMe, CONHMe, COONHEt, COO(CH₂)₂NEt₂,
COO(CH₂)₂NMe₂ or hydrogen and Z is hydrogen or COOH.

 95. The pharmaceutical composition according
to Claim 92 wherein at least three of R₁, R₂, R₃, R₄, R₅,
30 R₆, R₇ or R₈ is lower alkoxy.

1 96. The pharmaceutical composition according
to Claim 95 wherein at most six of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 ,
 R_7 or R_8 is lower alkoxy.

5 97. The pharmaceutical composition of Claim 95
wherein three of R_1 , R_2 , R_3 or R_4 are lower alkoxy.

98. The pharmaceutical composition according
to Claim 95 wherein R_1 is hydrogen and R_2 , R_3 , and R_4 are
lower alkoxy.

10 99. The pharmaceutical composition according
to Claim 92 wherein R_1 , R_2 and R_4 are independently
hydrogen or lower alkoxy;

R_3 is hydrogen, lower alkoxy, arylalkoxy,
loweralkyl carbonyloxy or $\text{OSi}(R_{10}R_{11}R_{12})$;

R_5 is hydrogen, halo or lower alkoxy;

15 R_6 and R_8 are independently hydrogen or lower
alkoxy;

R_7 is hydrogen, lower alkoxy, lower alkyl,
halo, lower alkyl carbonyloxy, $\text{OSi}(R_{10}R_{11}R_{12})$,
 $\text{Si}(R_{17})(R_{18})(R_{19})$, amino,

20 lower alkylamino, dilower alkylamino, $\text{NHC}-R_9$,
diloweralkylamino lower alkoxy, lower alkylthio,
mercapto or nitro;

25 R_{10} , R_{11} , R_{12} , R_{17} , R_{18} and R_{19} are independently
lower alkyl; and

R_9 is lower alkyl or hydrogen.

100. The pharmaceutical composition according
to Claim 92 wherein R_1 and R_5 are hydrogen.

30 101. The pharmaceutical composition according
to Claim 92 wherein R_1 and R_5 are hydrogen and R_2 , R_3 and
 R_4 are lower alkoxy.

102. The pharmaceutical composition according
1 to Claim 92 wherein R_1 and R_5 are hydrogen, R_2 , R_3 and R_4
are lower alkoxy and R_6 , R_7 and R_8 are independently
hydrogen, lower alkoxy, halo, amino, lower alkylamino,
dilower alkylamino, lower alkyl thio or lower alkyl.

5 103. The pharmaceutical composition according
to Claim 102 wherein R_1 , R_5 , R_6 and R_8 are hydrogen, R_4 ,
 R_5 and R_6 are independently lower alkoxy and R_7 is
hydrogen, lower alkoxy, halo, amino, lower alkylamino,
dilower alkylamino, lower alkyl or thio lower alkyl.

10 104. The pharmaceutical composition according
to Claim 102 or 103 wherein lower alkyl and lower alkoxy
contain.

1-3 carbon atoms.

15 105. The pharmaceutical composition according
to Claims 102 or 103 wherein lower alkyl is methyl and
lower alkoxy is methoxy.

106. The pharmaceutical composition according
to Claim 92 wherein X is cis $-HC=CH-$,

20 Y_1 and Z_1 are independently hydrogen, lower
alkyl, lower alkoxy, carboxy, lower carbalkoxy,
 $COONR_{13}R_{14}$, cyano, or $COOQNR_{15}R_{16}$;

R_{13} , R_{14} , R_{15} and R_{16} are independently hydrogen
or lower alkyl;

Q is lower alkylene;

25 R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are
independently hydrogen, lower alkyl, halo, amino, lower
alkylamino, diloweralkylamino, lower alkoxy, lower
arylalkoxy, cyano, aryloxy, mercapto, lower alkyl thio,
amino lower alkyl, carboxy, carbolower alkoxy, $CONHR_9$,
30 $NHCO(R_9)$, lower alkanoyl, nitro, CF_3 , lower alkyl
carbonyloxy, amino lower alkoxy, lower alkyl amino lower

1 alkoxy, dilower alkylamino lower alkoxy, amino lower
alkylene oxycarbonyl, lower alkylamino loweralkyleneoxy
carbonyl, dilower alkylamino lower alkylene oxy
carbonyl, $\text{OSi}(\text{R}_{10}\text{R}_{11}\text{R}_{12})$ or $\text{Si}(\text{R}_{17})(\text{R}_{18})(\text{R}_{19})$ and at least
5 two or R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 is loweralkoxy;
 R_9 is hydrogen or lower alkyl; and
 R_{10} , R_{11} , R_{12} , R_{17} , R_{18} and R_{19} are independently
lower alkyl.

107. The pharmaceutical composition according
to Claim 106 wherein at least three of R_1 , R_2 , R_3 , R_4 , R_5 ,
10 R_6 , R_7 or R_8 is lower alkoxy.

108. The pharmaceutical composition according
to Claim 106 wherein at most six of R_1 , R_2 , R_3 , R_4 , R_5 ,
 R_6 , R_7 or R_8 is lower alkoxy.

109. The pharmaceutical composition of Claim
15 106 wherein three of R_1 , R_2 , R_3 or R_4 are lower alkoxy.

110. The pharmaceutical composition according
to Claim 107 wherein R_1 is hydrogen and R_2 , R_3 , and R_4
are lower alkoxy.

111. The pharmaceutical composition according
20 to Claim 106 wherein R_1 , R_2 and R_4 are independently
hydrogen or lower alkoxy;

R_3 is hydrogen, lower alkoxy, arylalkoxy,
loweralkyl carbonyloxy or $\text{OSi}(\text{R}_{10}\text{R}_{11}\text{R}_{12})$;

25 R_5 is hydrogen, halo or lower alkoxy;

R_6 and R_8 are independently hydrogen or lower
alkoxy;

R_7 is hydrogen, lower alkoxy, lower alkyl,
halo, lower alkyl carbonyloxy, $\text{OSi}(\text{R}_{10}\text{R}_{11}\text{R}_{12})$,
30 $\text{Si}(\text{R}_{17})(\text{R}_{18})(\text{R}_{19})$, amino,

1 lower alkylamino, dilower alkylamino, $\text{NHC}-\overset{\text{O}}{\parallel}{\text{R}}_9$,
diloweralkylamino lower alkoxy, lower alkylthio,
mercapto or nitro;

5 R_{10} , R_{11} , R_{12} , R_{17} , R_{18} and R_{19} are independently
lower alkyl; and

R_9 is lower alkyl or hydrogen.

112. The pharmaceutical composition according
to Claim 106 wherein R_1 and R_5 are hydrogen.

10 113. The pharmaceutical composition according
to Claim 106 wherein R_1 and R_5 are hydrogen and R_2 , R_3
and R_4 are lower alkoxy.

114. The pharmaceutical composition according
to Claim 106 wherein R_1 and R_5 are hydrogen, R_2 , R_3 and R_4
15 are

lower alkoxy and R_6 , R_7 and R_8 are independently
hydrogen, lower alkoxy, halo, amino, lower alkylamino,
dilower alkylamino, lower alkyl thio or lower alkyl.

115. The pharmaceutical composition according to
20 Claim 106 wherein R_1 , R_5 , R_6 and R_8 are hydrogen, R_4 , R_5
and R_6 are independently lower alkoxy and R_7 is hydrogen,
lower alkoxy, halo, amino, lower alkylamino, dilower
alkylamino, lower alkyl thio or lower alkyl.

116. The pharmaceutical composition according
to Claims 114 or 115 wherein lower alkyl and lower
25 alkoxy contain 1-3 carbon atoms.

117. The pharmaceutical composition according
to Claims 114 or 115 wherein lower alkyl is methyl and
lower alkoxy is methoxy.

118. The pharmaceutical composition according
30 to Claim 13 wherein

1 X is cis HC=CH, R₁, R₅, R₆ and R₇ are H and R₂,
R₃, R₄ and R₇ is methoxy.

119. The pharmaceutical composition according
to Claim 13 wherein

5 X is cis CH=CH; R₁, R₅, R₇ and R₈ are H; R₂, R₃,
R₄ and R₆ are OCH₃;

X is cis CH=CH; R₁, R₆ and R₈ are H; R₅ is 2-
Cl; R₂, R₃, R₄ and R₇ are OCH₃;

10 X is cis CH=CH; R₁, R₅, R₆ and R₈ are H; R₇ is
Cl and R₂, R₃ and R₄ are OCH₃;

X is cis CH=CH; R₁, R₅, R₆ and R₈ are H; R₇ is
Br, and R₂, R₃ and R₄ are OCH₃;

X is cis CH=CH; R₁, R₅, R₆ and R₈ are H; R₇ is
NMe₂, and R₂, R₃, R₄ are OCH₃;

15 X is cis CH=CH; R₁, R₅, R₆ and R₈ are H; R₇ is
OEt, and R₂, R₃ and R₄ are OCH₃;

X is cis CH=CH; R₁, R₅, R₆ and R₈ are H; R₇ is
OPr, and R₂, R₃ and R₄ are OCH₃;

20 X is cis CH=CH; R₁, R₅, R₆ and R₈ are H; R₇ is
SMe, and R₂, R₃ and R₄ are OCH₃;

X is cis CH=CH; R₁, R₅, R₆ and R₈ are H; R₇ is
Me, and R₂, R₃ and R₄ are OCH₃;

X is cis CH=CH; R₁, R₅, R₆ and R₈ are H; R₇ is
Et, and R₂, R₃ and R₄ are OCH₃;

25 X is cis CH=CH; R₁, R₅, R₆ and R₈ are H; R₇ is
iPr, and R₂, R₃ and R₄ are OCH₃;

X is CH₂CH₂; R₁, R₅, R₆ and R₈ are H; R₂, R₃, R₄
and R₇ are OCH₃; or

30 X is CHNH, R₁, R₅, R₆ and R₈ are H and R₂, R₃, R₄
and R₇ are OCH₃.

120. A method for treating cancer in an animal
which comprises administering to said animal in need of

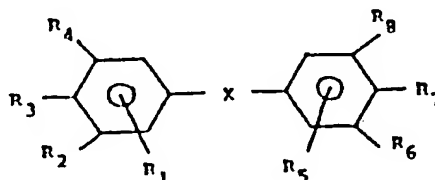
1 such treatment an anti-cancer effective amount of a
 1 compound according to Claim 1.

121. The method according to Claim 120 wherein
 said animal is a mammal.

5 122. The method according to Claim 121 wherein
 said mammal is human.

123. The compound having the formula:

10



15

wherein:

X is -NH-CH₂- or -CH₂NH-,

18 R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ are
 20 independently hydrogen, lower alkyl, halo, amino, lower
 21 alkylamino, diloweralkylamino, lower alkoxy, lower
 22 arylalkoxy, cyano, aryloxy, mercapto, lower alkyl thio,
 23 amino lower alkyl, carboxy, carbolower alkoxy, CONHR₉,
 24 NHCO(R₉), lower alkanoyl, nitro, CF₃, lower alkyl
 25 carbonyloxy, amino lower alkoxy, lower alkyl amino lower
 26 alkoxy, dilower alkylamino lower alkoxy,
 27 amino lower alkylene oxycarbonyl, lower alkylamino
 28 loweralkyleneoxy carbonyl, dilower alkylamino lower
 29 alkylene oxy carbonyl, OSi(R₁₀R₁₁R₁₂) or Si(R₁₇)(R₁₈)(R₁₉)
 30 and at least two of R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ is
 loweralkoxy;

R₉ is hydrogen or lower alkyl;

35

1 R_{10} , R_{11} , R_{12} , R_{17} , R_{18} and R_{19} are independently
lower alkyl.

124. The compound according to Claim 123 wherein
X is

5 $-\text{NH}-\text{CH}_2-$.

125. The compound according to Claim 123 wherein
X is CH_2NH .

126. The compound according to Claim 123 wherein
at least three of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 or R_8 are
lower alkoxy.

10 127. The compound according to Claim 126 wherein
three of R_1 , R_2 , R_3 or R_4 are lower alkoxy.

128. The compound according to Claim 127 wherein
 R_2 , R_3 and R_4 are lower alkoxy.

15 129. The compound according to Claim 123 wherein
 R_1 , R_2 and R_4 are independently hydrogen or lower alkoxy;

R_3 is hydrogen, lower alkoxy, arylalkoxy,
loweralkyl carbonyloxy or $\text{OSi}(R_{10}R_{11}R_{12})$;

R_5 is hydrogen, halo or lower alkoxy;

20 R_6 and R_8 are independently hydrogen or lower
alkoxy;

R_7 is hydrogen, lower alkoxy, lower alkyl,
halo, lower alkyl carbonyloxy, $\text{OSi}(R_{10}R_{11}R_{12})$,
 $\text{Si}(R_{17})(R_{18})(R_{19})$, amino,

25 O
 \parallel
lower alkylamino, dilower alkylamino, $\text{NHC}-R_9$,
diloweralkyl-amino lower alkoxy, lower alkylthio,
mercapto or nitro;

30 R_{10} , R_{11} , R_{12} , R_{17} , R_{18} and R_{19} are independently
lower alkyl; and

R_9 is lower alkyl or hydrogen.

130. The compound according to Claim 123 wherein
1 lower alkoxy is methoxy.

131. The compound according to Claim 123 wherein
R₁ and R₅ are hydrogen.

5 132. The compound according to Claim 123 wherein
R₁ and R₅ are hydrogen and R₂, R₃, R₄, R₅, R₆, R₇ and R₈
are hydrogen or lower alkoxy.

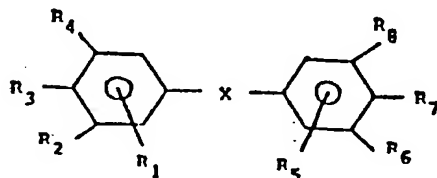
133. The compound according to Claim 132 wherein
R₂, R₃ and R₄ are lower alkoxy.

10 134. The compound according to Claim 132 wherein
lower alkoxy is methoxy.

135. The compound according to Claim 133 wherein
lower alkoxy is methoxy.

136. The compound having the formula

15



20

wherein X is $\begin{array}{c} \text{O} \\ \parallel \\ -\text{CNH}- \text{ or } -\text{NHCO}- \end{array}$;

25 R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ are
independently hydrogen, lower alkyl, halo, amino, lower
alkylamino, diloweralkylamino, lower alkoxy, lower
arylalkoxy, cyano, aryloxy, mercapto, lower alkyl thio,
amino lower alkyl, carboxy, carbolower alkoxy, CONHR₉,
30 NHCO(R₉), lower alkanoyl, nitro, CF₃, lower alkyl
carbonyloxy, amino lower alkoxy, lower alkyl amino lower
alkoxy, dilower alkylamino lower alkoxy,

35

1 amino lower alkylene oxycarbonyl, lower alkylamino
loweralkyleneoxy carbonyl, dilower alkylamino lower
alkylene oxy carbonyl, $\text{OSi}(\text{R}_{10}\text{R}_{11}\text{R}_{12})$ or $\text{Si}(\text{R}_{17})(\text{R}_{18})(\text{R}_{19})$
and at least two of $\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5, \text{R}_6, \text{R}_7$ and R_8 is
loweralkoxy;

5 R_9 is hydrogen or lower alkyl;
 $\text{R}_{10}, \text{R}_{11}, \text{R}_{12}, \text{R}_{17}, \text{R}_{18}$ and R_{19} are independently
lower alkyl.

137. The compound according to Claim 136
wherein X is $-\text{NHCO}-$.

10 138. The compound according to Claim 136
wherein X is $-\text{CONH}-$.

139. The compound according to Claim 136
wherein at least three of $\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5, \text{R}_6, \text{R}_7$ or R_8
are lower alkoxy.

15 140. The compound according to Claim 139
wherein three of $\text{R}_1, \text{R}_2, \text{R}_3$ or R_4 are lower alkoxy.

141. The compound according to Claim 140
wherein R_2, R_3 and R_4 are lower alkoxy.

20 142. The compound according to Claim 136
wherein R_1, R_2 and R_4 are independently hydrogen or lower
alkoxy;

R_3 is hydrogen, lower alkoxy, arylalkoxy,
loweralkyl carbonyloxy or $\text{OSi}(\text{R}_{10}\text{R}_{11}\text{R}_{12})$;

25 R_5 is hydrogen, halo or lower alkoxy;
 R_6 and R_8 are independently hydrogen or lower
alkoxy;

R_7 is hydrogen, lower alkoxy, lower alkyl,
halo, lower alkyl carbonyloxy, $\text{OSi}(\text{R}_{10}\text{R}_{11}\text{R}_{12})$,
 $\text{Si}(\text{R}_{17})(\text{R}_{18})(\text{R}_{19})$, amino,

30

1 lower alkylamino, dilower alkylamino, $\text{NHC}-\overset{\text{O}}{\parallel}{\text{R}}_9$,
 diloweralkyl-amino lower alkoxy, lower alkylthio,
 mercapto or nitro;

5 R_{10} , R_{11} , R_{12} , R_{17} , R_{18} and R_{19} are independently
 lower alkyl; and

R_9 is lower alkyl or hydrogen.

143. The compound according to Claim 136
 wherein lower alkoxy is methoxy.

10 144. The compound according to Claim 136
 wherein R_1 and R_5 are hydrogen.

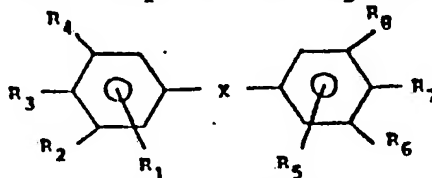
145. The compound according to Claim 136
 wherein R_1 and R_5 are hydrogen and R_2 , R_3 , R_4 , R_5 , R_6 , R_7
 and R_8 are hydrogen or lower alkoxy.

15 146. The compound according to Claim 145
 wherein R_2 , R_3 and R_4 are lower alkoxy.

147. The compound according to Claim 145
 wherein lower alkoxy is methoxy.

20 148. The compound according to Claim 146
 wherein lower alkoxy is methoxy.

149. The compound having the formula



25 wherein X is a cis ethylene radical of the formula
 $-(\text{Y}_1)\text{C}=\text{C}(\text{Z}_1)-$

Y_1 and Z_1 are independently hydrogen, lower
 alkyl, lower alkoxy, carboxy, lower carbalkoxy,
 30 $\text{COONR}_{13}\text{R}_{14}$, cyano, or $\text{COONR}_{15}\text{R}_{16}$;

R_{13} , R_{14} , R_{15} and R_{16} are independently hydrogen
 or lower alkyl;

1 Q is lower alkylene;
R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ are
independently hydrogen, lower alkyl, halo, amino, lower
alkylamino, diloweralkylamino, lower alkoxy, lower
5 arylalkoxy, cyano, aryloxy, mercapto, lower alkyl thio,
amino lower alkyl, carboxy, carbolower alkoxy, CONHR₉,
NHCO(R₉), lower alkanoyl, nitro, CF₃, lower alkyl
carbonyloxy, amino lower alkoxy, lower alkyl amino lower
alkoxy, dilower alkylamino lower alkoxy,
10 amino lower alkylene oxycarbonyl, lower alkylamino
loweralkyleneoxy carbonyl, dilower alkylamino lower
alkylene oxy carbonyl, OSi(R₁₀R₁₁R₁₂) or Si(R₁₇)(R₁₈)(R₁₉)
and at least two of R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ is
loweralkoxy;

R₉ is hydrogen or lower alkyl; and
15 R₁₀, R₁₁, R₁₂, R₁₇, R₁₈ and R₁₉ are independently
lower alkyl.

150. The compound according to Claim 149
wherein at least one of Y and Z is hydrogen.

151. The compound according to Claim 149
20 wherein Y is COOH, COOMe, CONHMe, COONHET, COO(CH₂)NEt₂,
COO(CH₂)₂NMe₂ or hydrogen and Z is hydrogen or COOH.

152. The compound according to Claim 149
wherein at least three of R₁, R₂, R₃, R₄, R₅, R₆, R₇ or R₈
is lower alkoxy.

25 153. The compound according to Claim 149
wherein at most six of R₁, R₂, R₃, R₄, R₅, R₆, R₇ or R₈ is
lower alkoxy.

154. The compound according to Claim 152
wherein three of R₁, R₂, R₃ or R₄ are lower alkoxy.

30

35

1 155. The compound according to Claim 149
wherein R_1 is hydrogen and R_2 , R_3 , and R_4 are lower
alkoxy.

5 156. The compound according to Claim 149
wherein R_1 , R_2 and R_4 are independently hydrogen or lower
alkoxy;

R_3 is hydrogen, lower alkoxy, arylalkoxy,
loweralkyl carbonyloxy or $\text{OSi}(R_{10}R_{11}R_{12})$;

R_5 is hydrogen, halo or lower alkoxy;

10 R_6 and R_8 are independently hydrogen or lower
alkoxy;

R_7 is hydrogen, lower alkoxy, lower alkyl,
halo, lower alkyl carbonyloxy, $\text{OSi}(R_{10}R_{11}R_{12})$,
 $\text{Si}(R_{17})(R_{18})(R_{19})$, amino,

15 lower alkylamino, dilower alkylamino, $\text{NHC}-R_9$,
diloweralkyl-amino lower alkoxy, lower alkylthio,
mercapto or nitro;

20 R_{10} , R_{11} , R_{12} , R_{17} , R_{18} and R_{19} are independently
lower alkyl; and

R_9 is lower alkyl or hydrogen.

157. The compound according to Claim 149
wherein R_1 and R_5 are hydrogen.

25 158. The compound according to Claim 149
wherein R_1 and R_5 are hydrogen and R_2 , R_3 and R_4 are lower
alkoxy.

30 159. The compound according to Claim 149
wherein R_1 and R_5 are hydrogen, R_2 , R_3 and R_4 are lower
alkoxy and R_6 , R_7 and R_8 are independently hydrogen,
lower alkoxy, halo, amino, lower alkylamino, dilower
alkylamino, lower alkyl thio or lower alkyl.

1 160. The compound according to Claim 159
wherein R_1 , R_5 , R_6 and R_8 are hydrogen, R_4 , R_5 and R_6 are
independently lower alkoxy and R_7 is hydrogen, lower
alkoxy, halo, amino, lower alkylamino, dilower
alkylamino, lower alkyl thio or lower alkyl.

5 161. The compound according to Claim 159 or 160
wherein lower alkyl and lower alkoxy contain 1-3 carbon
atoms.

10 162. The compound according to Claim 159 or 160
wherein lower alkyl is methyl and lower alkoxy is
methoxy.

 163. The compound according to Claim 149
wherein X is cis $-HC=CH-$;

15 R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are
independently hydrogen, lower alkyl, halo, amino, lower
alkylamino, diloweralkylamino, lower alkoxy, lower
arylalkoxy, cyano, aryloxy, mercapto, lower alkyl thio,
amino lower alkyl, carboxy, carbolower alkoxy, $CONHR_9$,
20 $NHCO(R_9)$, lower alkanoyl, nitro, CF_3 , lower alkyl
carbonyloxy, amino lower alkoxy, lower alkyl amino lower
alkoxy, dilower alkylamino lower alkoxy,
amino lower alkylene oxycarbonyl, lower alkylamino
loweralkyleneoxy carbonyl, dilower alkylamino lower
alkylene oxy carbonyl, $OSi(R_{10}R_{11}R_{12})$ or $Si(R_{17})(R_{18})(R_{19})$
and at least two of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 is
25 loweralkoxy;

R_9 is hydrogen or lower alkyl; and

R_{10} , R_{11} , R_{12} , R_{17} , R_{18} and R_{19} are independently
lower alkyl.

30 164. The compound according to Claim 163
wherein at least three of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 or R_8
is lower alkoxy.

- 1 165. The compound according to Claim 163
 wherein at most six of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 or R_8 is
 lower alkoxy.
166. The compound according to Claim 163
 wherein three of R_1 , R_2 , R_3 or R_4 are lower alkoxy.
- 5 167. The compound according to Claim 163
 wherein R_1 is hydrogen and R_2 , R_3 , and R_4 are lower
 alkoxy.
168. The compound according to Claim 163
 wherein R_1 , R_2 and R_4 are independently hydrogen or lower
 10 alkoxy;
 R_3 is hydrogen, lower alkoxy, arylalkoxy,
 loweralkyl carbonyloxy or $\text{OSi}(R_{10}R_{11}R_{12})$;
 R_5 is hydrogen, halo or lower alkoxy;
 R_6 and R_8 are independently hydrogen or lower
 15 alkoxy;
 R_7 is hydrogen, lower alkoxy, lower alkyl,
 halo, lower alkyl carbonyloxy, $\text{OSi}(R_{10}R_{11}R_{12})$,
 $\text{Si}(R_{17})(R_{18})(R_{19})$, amino,
 20 lower alkylamino, dilower alkylamino, $\text{NHC}-R_9$,
 diloweralkyl-amino lower alkoxy, lower alkylthio,
 mercapto or nitro;
 R_{10} , R_{11} , R_{12} , R_{17} , R_{18} and R_{19} are independently
 25 lower alkyl; and
 R_9 is lower alkyl or hydrogen.
169. The compound according to Claim 163
 wherein R_1 and R_5 are hydrogen.
170. The compound according to Claim 163
 30 wherein R_1 and R_5 are hydrogen and R_2 , R_3 and R_4 are lower
 alkoxy.

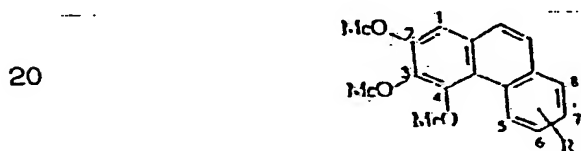
171. The compound according to Claim 163 wherein R_1 and R_5 are hydrogen, R_2 , R_3 and R_4 are lower alkoxy and R_6 , R_7 and R_8 are independently hydrogen, lower alkoxy, halo, amino, lower alkylamino, dilower alkylamino, lower alkyl thio or lower alkyl.

172. The compound according to Claim 163 wherein R_1 , R_5 , R_6 and R_8 are hydrogen, R_4 , R_5 and R_6 are independently lower alkoxy and R_7 is hydrogen, lower alkoxy, halo, amino, lower alkylamino, dilower alkylamino, lower alkyl thio or lower alkyl.

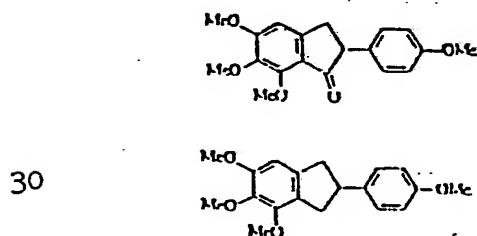
173. The compound according to Claim 171 or 172 wherein lower alkyl and lower alkoxy contain 1-3 carbon atoms.

174. The compound according to Claim 171 or 172 wherein lower alkyl is methyl and lower alkoxy is methoxy.

175. The compound selected from the group consisting of:



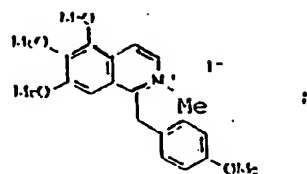
25 wherein R is C_{1-4} lower alkoxy;



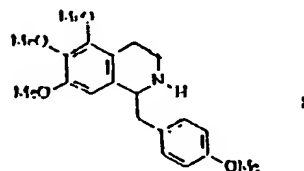
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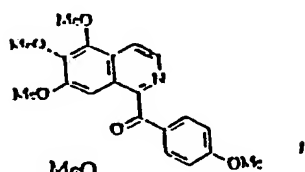
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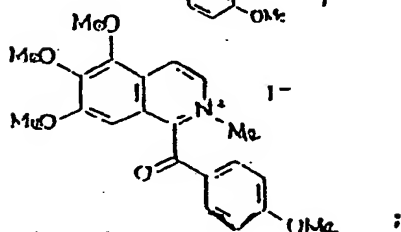
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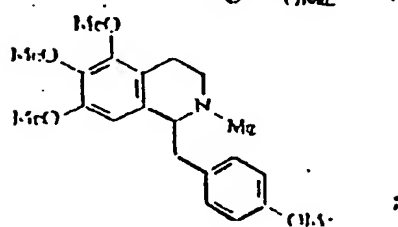
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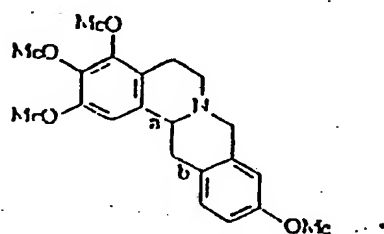
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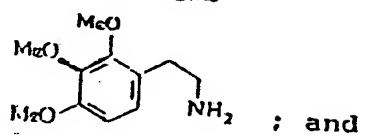
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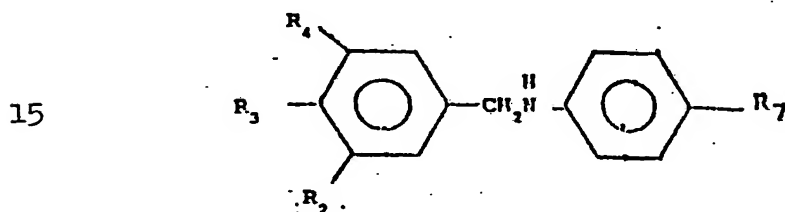
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1 176. A pharmaceutical composition comprising a
pharmaceutically effective amount of a compound in
accordance with Claim 175 and a pharmaceutical carrier
thereof.

5 177. A method of treating cancer in an animal
which comprises administering to an animal in need of
such treatment an anticancer effective amount of a
compound according to Claim 175.

10 178. The pharmaceutical composition of Claim 1
wherein X is CH_2NH or NHCH_2 .

179. The pharmaceutical composition of Claim 1
wherein the compound has the formula:



20 or pharmaceutically acceptable salts.

180. The pharmaceutical composition according to
Claim 179 wherein R_2 , R_3 , and R_4 are lower alkoxy and R_7
is hydrogen, lower alkyl, thioloweralkyl, lower alkoxy,
halo, or CF_3 .

25 181. The pharmaceutical composition of Claim 180
wherein R_2 , R_3 and R_4 are methoxy.

182. The pharmaceutical composition according to
Claim 180 wherein R_7 is methyl, ethyl, halo, thiomethyl,
methoxy, ethoxy or CF_3 .

30 183. The pharmaceutical composition according to
Claim 181 wherein R_7 is methyl, ethyl, halo, thiomethyl,
methoxy, ethoxy or CF_3 .

184. The pharmaceutical composition according to Claim 182 wherein R_1 is methyl, ethyl, bromo, chloro, iodo, thiomethyl, methoxy or CF_3 .

185. The pharmaceutical composition according to Claim 183 wherein R_1 is methyl, ethyl, bromo, chloro, iodo, thiomethyl, methoxy or CF_3 .

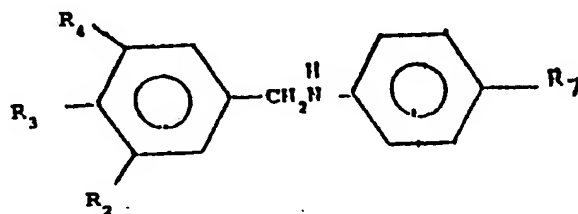
186. The pharmaceutical composition according to any one of Claims 178-185 wherein the compound is the pharmaceutical salt.

187. The pharmaceutical composition of Claim 186 wherein the salt is the hydrochloride.

188. The pharmaceutical composition of Claim 1 wherein the compound is 4-methyl-3',4',5'-trimethoxybenzylaniline or its pharmaceutically acceptable salt.

189. The pharmaceutical composition of Claim 188 wherein the compound is 4-methyl-3',4',5'-trimethoxybenzylaniline hydrochloride.

190. The compound of Claim 123 wherein the compound has the formula:



wherein R_2 , R_3 and R_4 are lower alkoxy and R_7 is hydrogen, lower alkyl, halo, thioloweralkyl, lower alkoxy, CF_3 , lower alkanoyl, formyl, carboxy, carboloweralkoxy, nitro, SO_3H or cyano.

1 191. The compound of Claim 190 wherein R₁ is
hydrogen, trifluoro-methyl, lower alkyl, halo, thio-
loweralkyl or lower alkoxy.

5 192. The compound of Claim 190 wherein R₁ is
lower alkyl, thio lower alkyl, lower alkoxy, CF₃, iodo,
bromo or chloro.

 193. The compound of Claim 190 wherein R₂, R₃,
and R₄ are methoxy and R₁ is lower alkyl, thioloweralkyl,
lower alkoxy, halo or CF₃.

10 194. The compound of Claim 193 wherein R₁ is CF₃,
methyl, thiomethyl, methoxy, ethyl, bromo, chloro, iodo,
or ethoxy.

 195. The compound of Claim 194 wherein R₁ is
methoxy, thiomethyl, iodo, chloro, bromo, methyl, ethyl
or CF₃.

15 196. The compound of Claim 192 wherein R₁ is
methyl, thiomethyl, methoxy, ethyl, bromo, chloro, iodo,
ethoxy or CF₃.

 197. The compound of Claim 196 wherein R₁ is
methoxy, thiomethyl, bromo, chloro, iodo, methyl, ethyl
or CF₃.

 198. The compound according to Claim 190 which
is 4-methyl-3',4',5'-trimethoxybenzylaniline or its
pharmaceutically acceptable salt.

25 199. The compound according to Claim 198 which
is 4-methyl-3',4',5'-trimethoxybenzylaniline
hydrochloride.

 200. The compound according to Claim 190 which
is 4-ethyl-N-(3',4',5'-trimethoxybenzylaniline or a
pharmaceutically acceptable salt thereof.

1 201. The compound according to Claim 190 wherein
the compound is 4-ethyl-N-(3',4',5'-
trimethoxybenzyl)aniline hydrochloride.

5 202. The pharmaceutical composition according to
Claim 179 where the compound is 4-ethyl-N-(3',4',5'-
trimethoxybenzyl)aniline or its pharmaceutically
acceptable salt.

10 203. The pharmaceutical composition according to
Claim 202 wherein the compound is 4-ethyl-N-(3',4',5'-
trimethoxybenzyl)aniline hydrochloride.

15 204. The pharmaceutical composition of Claim 179
wherein R_2 , R_3 and R_4 are lower alkoxy and R_1 is
hydrogen, CF_3 , lower alkyl, thioloweralkyl, lower
alkoxy, halo, nitro, lower alkanoyl, carboxy,
carboloweralkoxy, formyl, cyano or SO_3H .

20 205. A method for treating cancer in an animal
which comprises administering to said animal in need of
such treatment an anti-cancer effective amount of a
compound according to any of Claims 123-135 or Claims
190-201.

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INTERNATIONAL SEARCH REPORT

PCT/US 93/04807

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07C43/215; C07C69/157;	A61K31/09; C07C49/84;	C07C43/225; C07C205/35; C07C43/23 C07C217/58
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07C ; A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	JOURNAL OF MEDICINAL CHEMISTRY vol. 34, no. 8, August 1991, WASHINGTON US pages 2579 - 2588 M. CUSHMAN ET AL 'SYNTHESIS AND EVALUATION OF STILBENE AND DIHYDROSTILBENE DERIVATIVES AS POTENTIAL ANTICANCER AGENTS THAT INHIBIT TUBULIN POLYMERIZATION' see the whole document	1-23, 40-119, 123-174, 178-187, 190-197, 204
X	FR,A,2 336 923 (KAKEN CHEMICAL) 29 July 1977 see claims and page 17, compound nos. 74, 75 and 92	1,2,6,7, 10,13, 16,17, 20, 24-27,29
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
31 AUGUST 1993	- 9. 09. 93	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	WRIGHT M.W.	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	JOURNAL OF ORGANIC CHEMISTRY. vol. 31, no. 2, February 1966, EASTON US pages 516 - 520 S. KUBOTA ET AL 'THE STRUCTURE AND TOTAL SYNTHESIS OF TAKATONINE' see page 518, compounds VI and XII; document cited in the description ---	175
X	JOURNAL OF MEDICINAL CHEMISTRY vol. 24, no. 11, November 1981, WASHINGTON US pages 1348 - 1353 P. JACOB III ET AL 'SULFUR ANALOGUES OF PSYCHOMIMETIC AGENTS. MONOTHIO ANALOGUES OF Mescaline AND ISOMescaline' ---	175
X	CHEMICAL ABSTRACTS, vol. 105, no. 15, 13 October 1986, Columbus, Ohio, US; abstract no. 134202n, S. AL-KHALIL ET AL 'THE SYNTHESIS OF THALMICRINONE, A CONFIRMATION OF STRUCTURE' page 704 ;column 2 ; see abstract & J. NAT. PROD. vol. 48, no. 6, pages 989 - 991 ---	175
X	CHEMICAL ABSTRACTS, vol. 77, no. 5, 31 July 1972, Columbus, Ohio, US; abstract no. 28799f, Y. ISHIDA ET AL 'TAKATONINE RELATED COMPOUNDS. THEIR PHARMACOLOGICAL ACTION ON SMOOTH MUSCLE' page 15 ;column 2 ; see abstract & TOKUSHIMA DAIGAKU YAKUGAKU KENKYU NEMPO vol. 19, 1970, pages 17 - 21 ---	175, 176
X	'CHEMICAL ABSTRACTS ELEVENTH COLLECTIVE INDEX, CHEMICAL SUBSTANCES, OXYCELODEX-PHENOL, BUTYL', AMERICAN CHEMICAL SOCIETY see page 47923CS, column 1, phenanthrene, 2,3,4,5-tetramethoxy- and 2,3,4,7-tetramethoxy- ---	175

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claims No.
P,X	<p>JOURNAL OF MEDICINAL CHEMISTRY vol. 35, no. 12, 12 June 1992, WASHINGTON US pages 2293 - 2306 M. CUSHMAN ET AL 'SYNTHESIS AND EVALUATION OF ANALOGUES OF (Z)-1-(4-METHOXYPHENYL)-2- (3,4,5-TRIMETHOXYPHENYL)ETHENE AS POTENTIAL CYTOTOXIC AND ANTIMITOTIC AGENTS' see the whole document -----</p>	<p>1-35, 64-119, 149-176</p>

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 93/04807

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 120-122, 177, 205 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds/compositions.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9304807
SA 74717

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 31/08/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A-2336923	29-07-77	JP-A- 52083937	13-07-77
		JP-B- 59046205	10-11-84
		AU-B- 504411	11-10-79
		AU-A- 2071576	22-06-78
		BE-A- 850024	30-06-77
		DE-A- 2659580	14-07-77
		GB-A- 1556263	21-11-79
		NL-A- 7614567	05-07-77
		US-A- 4124726	07-11-78
		US-A- 4145444	20-03-79

FORM P007

EPO FORM P0079

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82